Applying Ontological Realism to Medically Unexplained Syndromes

Kristina Doing-Harris, Stephane M. Meystre, Matthew Samore, Werner Ceusters

Abstract

The past decade has witnessed an increased interest in what are called “medically unexplained syndromes” (MUS). We address the question of whether structuring the domain knowledge for MUS can be achieved by applying the principles of Ontological Realism in light of criticisms about their usefulness in areas where science has not yet led to insights univocally endorsed by the relevant communities. We analyzed whether the different perspectives held by MUS researchers can be represented without taking any particular stance and whether existing ontologies based on Ontological Realism can be further built upon. We did not find refutation of the applicability of the principles. We found the Ontology of General Medical Science and Information Artifact Ontology to provide useful frameworks for analyzing certain MUS controversies, although leaving other questions open.

Keywords:
Medically Unexplained Syndromes, Ontological Realism.

Introduction

The term “medically unexplained syndrome” (MUS) is used for constellations of symptoms characterized by lack of well-defined pathogenic pathways, while “medically unexplained symptom” (MU Symptom) is used for individual symptoms associated with a negative diagnostic evaluation. The estimates of the prevalence of MUS have varied across studies, depending in part upon definitions used [1,2]. Epidemiological analysis of MUS (in both its senses) is seriously hampered by lack of guidelines for the application of ICD-9-CM codes for “syndrome” or “signs, symptoms and ill-defined conditions” [3], inadequate application of diagnostic criteria [4], and discrepancies among criteria of classification systems such as ICD and DSM-IV [5]. The MUSs whose diagnostic criteria are the best established and most widely used are irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS) and fibromyalgia (FM). There is a need to identify MUS patients early since a delay in diagnosis is associated with poorer outcomes. Also, treatment for non-existent pathology may lead to iatrogenic symptoms. One problem is that descriptions of signs and symptoms are much richer in the non-structured parts of electronic health records (EHR) which contain clinical narratives. Therefore, the Salt Lake City VA, with the University of Utah, started developing an automated system for annotating IBS, CFS, and FM cases on the basis of free-text entries in EHRs. The goal is to identify those EHR entries that correspond to signs and symptoms exhibited by patients suffering from an MUS, thereby differentiating such entries from similar ones exhibited by patients without MUS, irrespective of whether a diagnosis of MUS could be determined by the use of some indicative diagnostic code. In line with standard practices for decision support system development in biomedicine [6], representation of the various types of knowledge required – domain knowledge, linguistic knowledge, knowledge about the structure of health records, and so forth [7] – is done by means of an ontology.

In this paper, we address the question of whether domain knowledge can be structured by applying the principles of Ontological Realism [8] as shown in Table 1. The use of Ontological Realism would allow the ontology to benefit from and contribute to the growing pool of OBO-Foundry ontologies that are mutually consistent and coherent through the application of these very principles [9]. However, the usefulness of these principles has been questioned [10], specifically in areas where science has not yet led to insights univocally endorsed by the relevant communities [11]. The latter applies without any doubt to the domain of MUS as witnessed, for example, by the claim that scientific knowledge with regard to these conditions has not proceeded any further than that medical science continues to be concerned with naming something that the science still fails to understand [12].

Materials and Methods

We performed a literature review of 31 papers that refer to MU Symptoms (generally in connection with somatoform disorder [SD]), without specifying a specific constellation of symptoms; as well as 21 papers that address specific types of MUS. Four of these papers were written in the last two years in response to the new edition of DSM. We identify the general agreements and controversies requiring representation in our domain ontology by comparing and contrasting these 52 papers.

We studied the principles of Ontological Realism [8], criticisms thereof [10], and suggested solutions [13]. We specifically assessed – re: principle P3 (Table 1) – whether the Ontology of General Medical Science (OGMS, http://code.google.com/p/ogms/) which represents entities DISEASE, DISORDER, SIGN, SYMPTOM, CLINICAL PICTURE, DIAGNOSIS, etc. [14], and the Information Artifact Ontology (IAO), which provides an overarching perspective on entities such as TERMINOLOGIES, CLASSIFICATION SYSTEMS, and DIAGNOSTIC CRITERIA [15], could serve as feeder ontologies. We used the insight obtained to outline the conditions and on-

1 When terms are printed in small caps they are used in a technical sense as defined in an OBO-Foundry ontology.
Ontology design criteria under which the issues identified in the literature can be resolved.

**Table 1 - Main principles of Ontological Realism [8]**

<table>
<thead>
<tr>
<th>Principles for Reference Ontologism</th>
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<tr>
<td><strong>P1</strong> Reference ontology principle: a reference ontology should cover the terminological content of the settled portions of a given scientific discipline. It should include only general terms, which are assumed to denote corresponding universals in reality and assertions of certain relations between instances thereof.</td>
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<td><strong>P2</strong> Principle of consistency with established science: the assertions of which a reference ontology consists, at any given stage, should be consistent with the best available settled science that is current at that stage.</td>
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<td><strong>P3</strong> Principle of instantiation: a term should be included in a reference ontology only if experimental evidence indicates that referent instances exist in reality.</td>
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<td><strong>P4</strong> Principle of asserted single inheritance: each reference ontology module should be built as an asserted mono-hierarchy.</td>
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**Principles applying to any realism-based ontology**

| P5 Application ontology principle: in areas where research is still exploratory and results provisional, application ontologies are to be built as far as possible as extensions of corresponding reference ontologies. |
| P6 Ontology path dependence principle: decisions made by the creators of an ontology should, as far as possible, be made based on the degree to which they advance the consistency of that ontology, with respect to existing reference ontologies from relevant domains. |
| P7 Principle of Aristotelian definitions: any term ‘A’ asserted to have parent term ‘B’, should be defined as ‘A=def. a B which C’, where ‘C’ expresses some condition on those instances of B which fall within the A’s. |
| P8 Principle of obsolescence: if a term in an ontology fails in designation, then it must immediately be obsoleted. |

**Results**

Table 2 lists the areas in the **domain** of MUS, for which scientists have thus far not reached agreement about the state of a patient, who exhibits symptoms that are suggestive of MUS, or about how one should proceed to make a reliable diagnosis. These areas are thus not yet part of settled science and create challenges for an MUS reference ontology. Table 3 and Table 4 list some design recommendations with respect to representational units for an MUS ontology such that it satisfies the principles of Table 1, given the challenges identified in Table 2.

**Discussion**

**Do “MUS” and similar terms denote?**

The backbone of an ontology, in its most general sense, is a formally organized hierarchy of terms which for mainstream ontologies designate concepts and for realism-based reference ontologies designate universals (P1). Expressing the backbone and additional associative relationships in a formal

**Table 2 - Challenges for a realism-based MUS ontology**

| Debates about the pathophysiological basis: |
| C1 Whether MUS form a subclass of somatoform disorders, are separate clinical syndromes, or no syndromes at all [16], |
| C2 Whether patients, with MUS, have a pathology either (1) inside or (2) outside the brain alone, or (3) in both brain and other bodily structures simultaneously, or (4) have no pathology at all [17]. |

**Problems with coherence of diagnostic criteria [4]:**

| C3 Frequently updated whereby some patients classified by means of an earlier version become classified differently later without there being any significant change in their disease course, |
| C4 Criteria issued by distinct authors are such that the same patient would be classified differently, |
| C5 Some criteria classify patients with very distinct phenotypes in the same category. |

**Diagnosis strongly based on symptom severity [18]:**

| C6 Patients and physicians have been found to be reluctant consider psychosocial factors, resulting in exaggerating, downplaying or ignoring symptom severity. |

**Table 3 - Design recommendations and conclusions for a realism-based MUS ontology**

| R1 ‘MUS,’ whether in the meaning of medically unexplained symptom or syndrome, cannot be a representational unit in a reference ontology. |
| R2 The current OGMS definitions for SYNDROME and SIGN have shortcomings, which would make it risky to define ‘MUS’ terms on their basis. |
| R3 The OGMS’ representational units CLINICAL PICTURE and DIAGNOSIS are inspirational for defining similar classes relevant to MUS, but are not encompassing. |
| R4 Assessment instruments and diagnostic criteria sets for MUS are to be analyzed as composite representations whose components are about universals. |
| R5 An MUS ontology should be an application ontology. |

**Table 4 - Foundational units for an MUS ontology**

| CLINICAL REPRESENTATION =def. – A (IAO) REPRESENTATIONAL ARTIFACT of a PHENOTYPE that is inferred from the combination of laboratory, image, and clinical findings about a given patient. |
| UNEXPLAINED CLINICAL REPRESENTATION =def. – A CLINICAL REPRESENTATION that when used as input for an interpretive process does not lead to a DIAGNOSIS. |
| DIAGNOSIS OF MUS =def. – A (IAO) REPRESENTATION of the conclusion of an interpretive process that has as input an UNEXPLAINED CLINICAL REPRESENTATION of a given patient and as output an assertion to the effect that no DIAGNOSIS has been established.
representation language (i.e., OWL) is for both types of ontologies governed by the syntactic-semantic rules of the language being used. There are, however, major differences between each type of ontology in what classes they may represent.

For concept-based ontologies, classes represent “concepts” and there are no rules or restrictions for what may serve as concepts. In this context, concepts are artifacts created by cognitive beings; therefore, whatever one can think of is acceptable [19]. The terms “medically unexplained symptom” and “medically unexplained syndrome,” together with their respective definitions from the literature, i.e., “symptoms that after investigation, cannot be explained by an underlying organic problem” for the former [2] and “constellations of medically unexplained symptoms that co-occur in consistent patterns” for the latter [20], are thus acceptable in concept-based ontologies. The problem with these definitions is that they ascribe to the symptom, and respectively syndrome, some feature which in reality is a feature of scientists: that they don’t know something [21].

Universals, in contrast, are not created but are discovered, in medicine through the advance of science (P3). In the first place, the question here is whether there exist universals, which are designated by the terms “medically unexplained symptom” and “medically unexplained syndrome.” If that is the case, a second question is how these universals relate to universals of which the existence has already been discovered. On the other hand, if no such universals exist, what might these terms then designate, under a realist perspective?

While scientific theories are being established and tested (using, for instance, the scientific method) as well as after theories are considered proven, it might well be that in communications among scientists terms are used that make sense in context, yet do not denote anything individually. These terms also may not denote what one would expect from a linguistic-semantic analysis of the term. For example, it is not true that because a statement such as “this patient has an absent nipple” is an accurate description of some portion of reality, that the term “absent nipple” denotes a special kind of nipple.

We begin our discussion with MU Symptoms, as they are, by definition, the basis for MUS. Clearly, principle P1 is a stronger requirement than P3. P3 is satisfied for the term “medically unexplained symptom” whenever it is used to denote some existing particular symptom (to which we assign unique identifier #1). Such as, for instance, the unexplainable orofacial pain the patient with unique identifier #2 has suffered from since last year. This is so irrespective of whether #1 can be explained according to the current state of the art in medicine. If it could, the term “unexplained symptom” would not be the best possible term from a terminological perspective because of its lack of face value [22]; despite the fact that it denotes something real, namely #1. P1, in contrast, is satisfied only if there would be some universal that is instantiated by all and only particulars that are similar to #1. Thus, only if there were symptoms that were always medically unexplained, i.e., cannot be other than being medically unexplained, and if things that were medically unexplained were always symptoms, the term “medically unexplained symptom” would denote a universal. Following the Ontological Realism principles of what counts as a universal [8], there is no such universal at all. #1 is rather an instance of the universal denoted by the term “pain.”

However, it is possible to use “medically unexplained symptom” as a term for a Defined Class (DC), i.e., a grouping of particulars that enjoy similarity in features which are selected by fiat [23], that feature being that patients in which no pathology could be detected experienced the symptoms.

In line with P6, it is worth investigating whether such a DC could be proposed using OGMS. The OWL version of OGMS contains the representational units “symptom” (defined slightly differently than in [14]) and “syndrome” (absent in [14]). The former denotes a subtype of ENTITY and is defined as “a QUALITY of a patient that is observed by the patient or a PROCESSUAL ENTITY experienced by the patient, either of which is hypothesized by the patient to be a realization of a DISEASE,” while the latter denotes a subtype of QUALITY with the definition “a pattern of SIGNS and SYMPTOMS that typically co-occur.” The problem is that these definitions do not satisfy P4 and P7; the former because it contains a disjunction (A is a B or C) and the latter because “pattern” is nowhere defined. OGMS has more work to do here and until it is done, it is unsafe to build further on these terms. This problem led us to formulate recommendation R2. If R2 is heeded, “MUS” terms can be defined as DCs and then figure as representational units in an application ontology in line with P5 and P6; hence recommendation R5.

Medically unexplained clinical pictures

As shown in Table 5, OGMS has adequate definitions for descriptions (CLINICAL PICTURE and DIAGNOSIS) about what is happening within a given patient (in terms of PHENOTYPE).

<table>
<thead>
<tr>
<th>Table 5 - Core OGMS definitions</th>
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<tr>
<td>CLINICAL PICTURE =def. – A REPRESENTATION of a CLINICAL PHENOTYPE that is inferred from the combination of laboratory, image and clinical findings about a given patient.</td>
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<tr>
<td>DIAGNOSIS =def. – A REPRESENTATION of the conclusion of an interpretive process that has as input a CLINICAL PICTURE of a given patient and as output an assertion to the effect that the patient has a DISEASE of such and such a type.</td>
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<tr>
<td>DISORDER =def. – A MATERIAL ENTITY that is part of an EXTENDED ORGANISM and is formed by a causally relatively isolated combination of physical components that is (a) clinically abnormal and (b) maximal, in the sense that it is not a part of some larger such combination.</td>
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<tr>
<td>PHENOTYPE =def. – A (combination of) BODILY FEATURE(s) of an ORGANISM determined by the interaction of its genetic make-up and environment.</td>
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<tr>
<td>CLINICAL PHENOTYPE =def. – A clinically abnormal PHENOTYPE.</td>
</tr>
<tr>
<td>DISEASE PHENOTYPE =def. – A CLINICAL PHENOTYPE that is characteristic of a single DISEASE.</td>
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Descriptions themselves are, obviously, not on the side of the patient, but about something on the side of the patient while being on the side of clinicians, medical records, reports, and so forth. The entities described in Table 5 all rely directly or indirectly on the definition of clinically abnormal, which is based on three criteria: (1) not being part of the life plan for an organism of the relevant type (unlike aging or pregnancy), (2) being causally linked to an elevated risk either of pain or other feelings of illness, or of death or dysfunction, and (3) being such that the elevated risk exceeds a certain threshold level [14]. Since both DIAGNOSIS and CLINICAL PICTURE are defined in...
terms of interpretation and inference, it seems defendable to create DCs, which limit the extension of each of the former to the effect that some part of the interpretation and inference processes failed to provide an acceptable explanation. A lot of caution is, however, required. The question is whether challenges C1, C2 and C6 – in light of principles P1 and P2 – prevent the use of CLINICAL PICTURE as a basis for the definition of what could be named “unexplained clinical picture.”

C6 cautions us that exaggerating symptom severity, whether by the patient or the clinician, might make the threshold for abnormality seem to have been crossed, while it is not. In both cases there would be no CLINICAL PHENOTYPE involved, although patient and clinician might believe otherwise. C1 and C2 require caution because it is not yet established that all patients asserted to have MUS do indeed have an underlying pathology; for a PHENOTYPE to be a CLINICAL PHENOTYPE there must be something clinically abnormal in the sense just defined. Here “pathology” is taken from the MUS literature and understood to be equivalent to OGMS’ DISORDER. Malingering, an extreme example of C6, falls clearly outside that definition. Patients who are overanxious about phenomena that are not clinically abnormal do, however, have a clinically abnormal BODILY FEATURE, not the phenomena they are worried about, but the anxiety itself.

An open question re C2 is whether it is possible for a patient to exhibit a CLINICAL PHENOTYPE without there being an underlying DISORDER. In [14] this seems to be ruled out, not by the definitions as such, but by means of the example given in the following paragraph: “When, for example, there is a persistent elevated level of glucose in the blood, this is because (1) some physical structure or substance in the organism is disordered (e.g. loss of beta cells in pancreatic islets) as a result of which (2) there exists a disposition (diabetes) for the organism to act in a certain abnormal way. The disposition in question is realized by pathological processes (diabetic nephropathy) including manifestations that can be recognized as signs of the disorder.” The example is used to clarify the view of DISEASE as resting in every case on some (perhaps as yet unknown) physical basis [24]. Any bodily feature, whether clinically abnormal, also rests on a physical basis. The important question to be answered by domain experts, not by ontologists, is whether there are patients who exhibit clinically abnormal bodily features of which the physical basis is not a DISORDER and which of these are what MUS experts denote by the term “MUS.”

Whatever is the case, there is nothing in Ontological Realism that would not allow either possibility to be expressed. Because the question remains currently unanswered, it is not possible to represent medically unexplained clinical pictures as special cases of CLINICAL PICTURE.

At this point, remaining faithful to the principles of Realism requires looking not only at the patient side, but also at the physicians’ side, as that is where the lack of an explanation is occurring. Our definitions with regard to physician representations are built via the IAO feeder ontology. The proposals expressed in Table 4 are inspired by the OGMS definition of CLINICAL PICTURE (although it cannot be used for the preceding reason) and avoid these problems (R3), thereby still satisfying P7. The replacement of CLINICAL PICTURE with CLINICAL REPRESENTATION, as defined, allows instances thereof to be about normal or abnormal PHENOTYPES, and for the latter to include both CLINICAL and DISEASE PHENOTYPES. The definition for UNEXPLAINED CLINICAL REPRESENTATION remains neutral about whether the inexplicability is due to (1) lack of knowledge and/or skills of the entity which is the agent of the interpretive process, (2) the state of the art being such that the underlying disease cannot be detected, or (3) there being no underlying disease at all (C2). The use of REPRESENTATIONAL ARTIFACT – following the proposed IAO definition thereof as “an information content entity which is believed to represent a portion of reality external to the representation” – instead of REPRESENTATION further allows instances of CLINICAL REPRESENTATIONS to be inaccurate, despite being believed to be accurate. The definition of CLINICAL REPRESENTATION – a representational unit which we believe should become part of OGMS – allows assertions such as “this patient’s clinical representation is perfectly normal” to be made. Doing so with CLINICAL PICTURE would contain a contradiction.

Diagnosis and diagnostic criteria

The proposed definition for DIAGNOSIS of MUS highlights the fact that MUS is a diagnosis of exclusion. Organic illness must be excluded as far as possible before a patient is diagnosed with a MUS. However, this exclusion cannot be absolute due to the existing limitations of understanding of possible underlying pathophysiological changes and organic disease [2]. The definition might at first sight seem strange for containing a contradiction: the diagnosis being that there is no diagnosis. However, DIAGNOSIS is used in the strict technical sense as defined in OGMS, thus explicitly referring to an assertion involving a type of DISEASE. Note also that DIAGNOSIS of MUS is not defined as being a DIAGNOSIS.

Research in MUS is quickly evolving, but not in a concerted way. A concerted effort could be achieved by using standard assessment instruments and diagnostic criteria. Such standards are being developed but many inconsistencies exist among them. In studies with direct access to patients and their physicians it was, for instance, found that 16% of patients with a diagnosis of FM did not meet the American College of Rheumatology (ACR) criteria, while 2% met the criteria, but did not have a diagnosis of FM [4]; and that when using two validated FM questionnaires, 47% and 34.8% of rheumatology clinic patients screened positive for FM, while only 10.6% had a diagnosis of FM [25]. In recruiting patients for a CFS study using primary care referral, 35% of patients with a CFS diagnosis did not actually meet the positive diagnostic criteria for CFS [26]. Of 73 patients who met the Rome II criteria for IBS, only seven were found to have a diagnosis of IBS [27].

The goal of an MUS ontology, in relation to these issues, should not be to judge which criteria are right or wrong, but rather to provide a mechanism for keeping track of the various ways in which criteria from distinct criteria sets overlap, are inconsistent, evolve over time, and so forth. We propose to achieve these goals by representing diagnostic criteria sets and validated questionnaires as composite representations as defined in the IAO [15] and to break these compositions down to the level of terms and phrases that denote entities which can be classified using the OGMS (R4).

Conclusion

Our research did not reveal any indications that the principles of Ontological Realism make the latter inadequate for application to MUS. While elements of IAO can be used to construct the representations used by physicians in thinking and writing about MUS, OGMS was however found to leave certain questions unanswered, most importantly the precise relationships between clinical phenotype and disorder. This makes it difficult, if currently not impossible, for MUS experts to formulate hypotheses about the nature of MUS in terms of OGMS.
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