EBioMedicine 4 (2016) 191–196

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Enabling Precision Medicine With Digital Case Classification at the Point-of-Care☆

Patrick Obermeier [a,b], Susann Muehlhans [a,b], Christian Hoppe [a,b], Katharina Karsch [a], Franziska Tief [a,b], Lea Seeber [a,b], Xi Chen [a,b], Tim Conrad [c], Sindy Boettcher [d], Sabine Diedrich [d], Barbara Rath [a,b,*]

[a] Department of Pediatrics, Charité University Medical Center Berlin, Germany
[b] Vienna Vaccine Safety Initiative, Berlin, Germany
[c] Department of Mathematics and Computer Sciences, Free University Berlin, Germany
[d] National Reference Centre for Poliomyelitis and Enteroviruses, Robert Koch Institute, Berlin, Germany

ARTICLE INFO

Article history:
Received 29 October 2015
Received in revised form 23 December 2015
Accepted 8 January 2016
Available online 12 January 2016

Keywords:
Encephalitis
Meningitis
ADEM
Surveillance
Mobile health
Data standards

ABSTRACT

Infectious and inflammatory diseases of the central nervous system are difficult to identify early. Case definitions for aseptic meningitis, encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM) are available, but rarely put to use. The VACC-Tool (Vienna Vaccine Safety Initiative Automated Case Classification-Tool) is a mobile application enabling immediate case ascertainment based on consensus criteria at the point-of-care. The VACC-Tool was validated in a quality management program in collaboration with the Robert-Koch-Institute. Results were compared to ICD-10 coding and retrospective analysis of electronic health records using the same case criteria. Of 68,921 patients attending the emergency room in 10/2010–06/2013, 11,575 were hospitalized, with 521 eligible patients (mean age: 7.6 years) entering the quality management program. Using the VACC-Tool at the point-of-care, 180/521 cases were classified successfully and 194/521 ruled out with certainty. Of the 180 confirmed cases, 116 had been missed by ICD-10 coding, 38 misclassified. By retrospective application of the same case criteria, 33 cases were missed. Encephalitis and ADEM cases were most likely missed or misclassified. The VACC-Tool enables physicians to ask the right questions at the right time, thereby classifying cases consistently and accurately, facilitating translational research. Future applications will alert physicians when additional diagnostic procedures are required.

1. Introduction

Patients with acute infections of the central nervous system (CNS) or post-infectious neuroinflammatory disease may present with a variety of clinical signs and symptoms, which are often subtle or inconsistent (Granerod et al., 2010; Koelman and Mateen, 2015). This poses a major challenge in clinical practice, translational medicine, clinical trials, and surveillance settings. Actual case numbers may be underestimated delaying the detection of disease outbreaks and important safety signals (Zwaan et al., 2010; Kelly et al., 2013; Gundlapalli et al., 2007). The timely and accurate classification of clinical cases constitutes an important prerequisite for precision medicine and timely access to therapy (Gundlapalli et al., 2007; Hughes and Jackson, 2012; Duffy, 2015). The ability to gain access to accurate clinical data in real-time will enable healthcare providers and public health stakeholders to overcome barriers to therapeutic and diagnostic innovation (Duffy, 2015).

ADEM	acute disseminated encephalomyelitis
VACC-Tool	Vienna Vaccine Safety Initiative Automated Case Classification Tool
CNS	Central nervous system
ICD	International Catalog of Diseases
EHR	electronic health records
QM	quality management
IRB	International review board
CDISC	Clinical data interchange standards consortium
FDA	Food and drug administration
PPA	positive percent agreement
NPA	negative percent agreement
ORA	overall rate of agreement
KL	Kullback Leibler
VAERS	Vaccine adverse event reporting system

For billing purposes and in routine care, ICD-codes (International Catalog of Diseases) are commonly used. ICD-codes do not distinguish

☆ This work obtained no outside funding.
* Corresponding author at: Department of Pediatrics, Charité University Medical Center Berlin, Augustenburger Platz 1, 13353 Berlin, Germany.
E-mail address: barbara.rath@gmail.com (B. Rath).

http://dx.doi.org/10.1016/j.ebiom.2016.01.008

between symptoms and diagnosis and are of limited value for systematic epidemiological research (St Germaine-Smith et al., 2012). For example, the same case of aseptic meningitis can be coded as either 'headache' or 'meningitis'.

ICD coding may thus result in considerable inconsistencies across sites, which can only be avoided if pre-defined case criteria are implemented universally (Zwaan et al., 2010; Gundlapalli et al., 2007; St Germaine-Smith et al., 2012; Horwitz and Yu, 1984; Rath et al., 2010; Prins et al., 2002). Standardized case criteria are particularly important as they have been developed for several complex neurological/autoimmune diseases, including aseptic meningitis, encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM) (Tapiainen et al., 2007; Sejvar et al., 2007). The application of these case criteria to electronic health records (EHR) has been shown to provide reproducible and consistent datasets as well as significant advantage over ICD-codes assigned in routine care (Zwaan et al., 2010; Muehlhans et al., 2012; Lankinen et al., 2004).

The same proof-of-concept study however, revealed that the retrospective application of standardized case criteria will result in a certain amount of missing data and indeterminate results with regard to the case definitions. This was the case whenever critical data that would be required for the case definition, had not been documented in the EHR (Rath et al., 2010). In other words, if a specific symptom such as 'headache' was not mentioned in the EHR, it will remain unclear to the assessor whether the patient did not have any headaches to begin with, or whether this question had not been raised during the physician encounter (Horwitz and Yu, 1984).

This observation lead to the recommendation that standardized case criteria should be implemented immediately at the point-of-care, when the patient is still accessible and all pertinent data can be obtained (Rath et al., 2010).

This translational research project aimed to evaluate whether immediate data collection with the use of innovative mobile applications might enable the physician to ask the right questions at the right time, thereby ensuring that all relevant information is collected at the point-of-care. This would increase the yield of cases that can either be classified and confirmed, or ruled out with certainty.

2. Methods

This study builds on a previous proof-of-concept study performed at a pediatric hospital in Switzerland, where standardized case criteria for aseptic meningitis, encephalitis, myelitis, and ADEM were applied retrospectively to hospital discharge summaries (Rath et al., 2010).

Now, the same four consensus case definitions (Tapiainen et al., 2007; Sejvar et al., 2007) were integrated a web-user interface (electronic clinical report form, CRF) as well as into a mobile application for the standardized case ascertainment at the point-of-care: the VACC-Tool (Vienna Vaccine Safety Initiative Automated Case Classification Tool, www.vi-vi.org). This innovative mobile application facilitating reliable case ascertainments at the patient's bedside, was designed based on the user-centered and solution-focused principles of Design Thinking (Seeber et al., 2015). The installation of the VACC-Tool on an Android-based handheld device using Java as a platform-independent programing language required approximately 5 min. For full transparency, audit trails and double data entry verification procedures were enabled, and data entry was restricted to authorized personnel only. Following the instructions of the Tool, anonymized datasets required for the respective case definitions were collected within approximately 20 min at the point-of-care. A dynamic adaptation system with subordinate questions linked to previously provided clinical information contributed to time-efficient assessments using the VACC-Tool. Automated algorithms compared the collected data with the criteria of published case definitions for meningitis, encephalitis, myelitis, and ADEM (Tapiainen et al., 2007; Sejvar et al., 2007). Results were provided immediately at the patient's bedside. In accordance with the published case definitions, cases were classified into three distinct levels of diagnostic certainty, with Level 1 being closest to gold standard, Levels 2 and 3 being less stringent but still evident. Level 4 represented a case with insufficient data, whereas Level 5 indicated a definitive "rule-out" (Tapiainen et al., 2007; Sejvar et al., 2007). Data entered into the VACC-Tool were fully compliant with standards issued by CDISC, the Clinical Data Interchange Standards Consortium (www.cdisc.org) (Souza et al., 2007). Mapping of all data elements to Clinical Data Acquisition Standards Harmonization (CDASH), Study Data Tabulation Model (SDTM) and the Biomedical Research Integrated Domain Group (BRIDG) Model enable instant data read-outs and exports, including for the automated submission of reports to regulatory authorities (Linder et al., 2010).

The VACC-Tool was available as a web user interface (eCRF) as well as a mobile application and was validated in the context of a quality management (QM) program at the Charité Department of Pediatrics in collaboration with the Robert-Koch-Institute in Berlin, Germany. All hospitalized children (0–18 years) with suspected CNS infection or inflammation meeting pre-defined QM entry criteria underwent standardized assessments by a specifically trained QM team using the VACC-Tool (Karsch et al., 2015). The QM team did not interfere with routine diagnostics or physician orders for laboratory or imaging studies. The QM program was approved by the Charité Institutional Review Board (IRB) (EA2/161/11). Informed consent procedures were waived by the IRB for the purpose of quality improvement. This work received no outside funding.

2.1. Retrospective Application of Pre-defined Case Criteria

For comparison, the same 521 clinical cases were re-classified applying the exact same case criteria and algorithms, but now retrospectively using routine EHR rather than queries raised by the QM staff at the point-of-care. As per consensus for algorithm-based datasets, any undocumented clinical signs or symptoms were reported as 'absent'. Data abstraction and double entry verification were performed by specifically trained data entry staff in compliance with Good Clinical Practice guidelines.

2.2. Validating a New Diagnostic Standard Against an Imperfect Reference Standard

Statistical analysis was performed using SPSS 21.0 software. In the absence of an accepted gold standard for the differential diagnosis of aseptic meningitis, encephalitis, myelitis, and ADEM, analyses were conducted according to Food and Drug Administration (FDA) guidelines and suggested terminologies for the reporting of results from studies evaluating diagnostic tests. Positive and negative percent agreement (PPA, NPA) and overall rates of agreement (ORA) were calculated to test a new diagnostic test against the imperfect reference standard (Fig. 1) (Rath et al., 2010).

Cross tabulations were used to compare the retrospective and prospective application of case criteria in the same cohort. The statistical power describes the probability of identifying an actual difference with the used statistical test. Following Chow et al. (2008), we calculated the power of our test to be larger than 0.99 with $n = 521$ and alpha $= 0.05$ (Chow et al., 2008).

Kappa coefficients were calculated to assess the coincidence of concordant/discordant results. P-values of less than 0.05 were considered statistically significant. Reported results were calculated with 95% confidence intervals based on the total sample size of 521, with a point estimate of 0.5 corresponding to the point of largest variance within a binomial distribution (Rath et al., 2010).