Epidemiologi genetik serta faktor risiko M. Tuberculosis yang resisten INH dan atau Rifampisin

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Abstrak

Tujuan: Untuk memahami mekanisme terjadinya resistensi terhadap obat antituberkulosis dengan mempergunakan pendekatan epidemiologik genetik.
Bahan dan metode penelitian:
Disain penelitian : kasus - kontrol.
Tempat: Rumah Sakit Persahabatan, Jakarta, Rumah Sakit Umum dr. M. Jamil, Sumatera Barat dan Rumah Sakit Umum dr. Wahidin Sudirohusodo, Makasar. Laboratorium Mikrobiologi FKUI, Jakarta, Lembaga Biologi Molekuler Eijkman, Jakarta dan Laboratorium Bioteknologi Universitas Padjajaran, Bandung.
Lama penelitian: 8 bulan (Januari 2002 - Agustus 2002).
Subjek penelitian: Masing-masing 279 sampel dahak yang sensitif dan resisten INH serta 36 sampel dahak yang sensitif dan resisten rifampisin.
Bahan: sampel dahak yang dikirim dari ketiga rumah sakit tersebut, diperiksa silang di laboratorium mikrobiologi FKUI, Jakarta, lalu diadakan pemeriksaan PCR dan sequencing di Lembaga Eijkman dan laboratorium BioteknoIogi Universitas Padjajaran, Bandung. Disamping itu dilakukan wawancara untuk mendapatkan keterangan mengenai kepatuhan berobat dan pengobatan yang tidak optimal. Data yang terkumpul dianalisis dengan menggunakan analisis uji statistik.
Hasil: Prevalensi resistensi terhadap INH dari ketiga propinsi berkisar dari 11,9 % sampai 15,6 %, prevalensi resistensi terhadap rifampisin berkisar dari 1,3 % sampai 1,6 % dan prevalensi resistensi ganda berkisar dari 0,6 % sampai 1,3 %, M. tuberculosis yang mengalami mutasi padagen katG dari ketiga propinsi didapatkan sebesar 60,2 % dan mempunyai kemungkinan risiko resisten terhadap INH sebesar 32,6 kali bila dibandingkan dengan M. tuberculosis yang tidak mengalami mutasi pada gen katG. M. tuberculosis yang resisten terhadap rifampisin dari ketiga propinsi menunjukkan bahwa semua M tuberculosis tersebut mengalami mutasi padagen rpoB, dimana mutasi gen rpoB pada kodon 516 (16,6 %), kodon 526 (63,8 %), kodon 529 dan kodon 531 masing-masing sebesar 5,5 %. Hal ini dapat dikatakan bahwa M. tuberculosis dari ketiga propinsi yang resisten terhadap INH dan rifampisin mengalami beraneka ragam jenis mutasi (diversity). Di ketiga propinsi, ketidakpatuhan penderita tuberkulosis berobat didapatkan sebesar 56,3 % pada M. tuberculosis resisten terhadap INH dan 75 % M. tuberculosis yang resisten terhadap rifampisin. 65,9 % penderita tuberkulosis yang mendapatkan pengobatan monotherapy mengalami resisten terhadap INH dan 75 % penderita tuberkulosis yang mendapatkan pengobatan tidak optimal mengalami resisten terhadap rifampisin. Mutasi baru gen rpoB pada kodon 529 ditemukan 2 buah yang berasal dari propinsi Jakarta dan propinsi Sumatera Barat. Mutasi baru ini tidak mempunyai dampak klinik dan biologis karena kedua kodon tersebut menyandi asam amino yang lama yaitu arginin.
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Genetic Epidemiological and Risk Factor Of M. Tuberculosis For Being Resistant To INH And Or RifampicinObjective of the Study: To understand the mechanisms of resistance to antituberculosis drugs by genetic epidemiological study.

Methods and materials of the study:
Study design: Case - control study.
Location: Persahabatan Hospital (Jakarta), M. Jamil General Hospital (West Sumatra), Wahidin Sudirohusodo General Hospital (South Sulawesi), Microbiology Laboratory FKUI (Jakarta), Eijkman Institute for biology molekuler (Jakarta) and Padjadjaran University Biotechnology Laboratory (West Java).
Duration of study: 8 months (January 2002 - August 2002).
Subject: 279 samples sputum each that were sensitive and resistant to NH, 36 sample sputum each that were sensitive and resistant to rifampiscin.
Material of study: - Sputum sample from three hospitals were sent to Microbiology Laboratory FKUI for crosschecking. Subsequently PCR examination and sequencing were performed in Eijkman Institute and Padjadjaran University Biotechnology Laboratory. In addition interviews were conducted to obtain information about patient compliance and optimal treatment. All data were subjected to statistical analysis.
Results: Resistance prevalence to INH from three provinces range from 11.9 % to 15.6 %; resistance prevalence to rifampicin 1.3 % to 1.6 % and multidrug resistant prevalence: 0.6 % to 1.3 %. Mutation on gene katG M. tuberculosis from three provinces were 60.2 % and have a probability resistance risk to INH 32.6 times compared to M. tuberculosis that didn't have mutation on gene katG. All M. tuberculosis resistant to rifampicin isolated from three provinces have a mutation on gene rpoB, on codon 516 (16.66 %), codon 526 (63.8%), codon 529 and codon 531 respectively 5.5 %. This situation showed that M. tuberculosis from three provinces resistant to INH and rifampicin have a diversity mutant, In the three provinces, non compliance from tuberculosis patient - were 56.3 % of M. tuberculosis resistant to INH and 75 % of M. tuberculosis resistant to rifampicin. INH monotherapy result in 65.9 % resistance and sub optimal treatment result in 75 % resistance to rifampicin. Two new mutations have been found in gene rpoB codon 529 from Jakarta and West Sumatra. And this new mutant has no clinical and biology impact because the two codons encode amino acid was same, is arginine.
Conclusions: Resistance prevalence to NH and or rifampicin in three provinces is significantly high despite a good health infrastructure. If this problem occurs in other provinces with difference geographic characteristic, demographic, socioeconomic and health infrastructure, most probably the resistance prevalence to INH and or rifampicin will be much be more pronounced. The development of resistance of M. tuberculosis to INH and or rifampicin is influenced by mutation on gene encoding enzyme catalase peroxidase (katG) and RNA Polymerise (rpoB). Non-compliance and sub optimal treatment are selection factors for katG and rpoB mutant.
Recommendations: It is recommended to continue a similar study in the other provinces with difference geographic, demographic, socio economic, health infrastructure and also other study with mutant. For the Department of Health it is recommended to accelerate methods of early detection of tuberculosis cases that are sensitive or resistant to antituberculosis drugs and monitoring system to record and to report tuberculosis cases from other public health services e.g. Private practices, non government clinics, hospitals and institution to ensure continuous availability and quality of controlled drugs.