ANOMALIA DE MAY-HEGGLIN COMO DIAGNÓSTICO DIFERENCIAL DE MACROTROMBOCITOPENIA: RELATO DO DIAGNÓSTICO DE UMA FAMÍLIA

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Introdução: A Anomalia de May-Hegglin (AMH) é uma rara condição genética autossômica dominante relacionada a mutações no gene MYH9 que codifica a cadeia pesada da miosina não muscular IIA (NMMHC-IIA). Esse defeito compõe um espectro de distúrbios além da AMH, como a Síndrome de Fechtner, Síndrome de Epstein e Síndrome de Sebastian. Essas doenças se caracterizam morfologicamente pela presença de plaquetopenia, macroplaquetase de inclusões citoplasmáticas basofílicas (Corpos Döhle) em neutrófilos. A depender do espectro clínico, os pacientes podem apresentar também falência renal, catarata e perda auditiva. **Relato de caso:** Paciente, 15 anos, sexo feminino, em acompanhamento hematológico desde os 3 anos de vida por trombocitopenia, a princípio considerada imune primária. Desde então, recebeu tratamentos direcionados a essa hipótese diagnóstica como pulsoterapia com corticóide, imunoglobulina e azatioprina. Apresentava baixa resposta, com manutenção de contagem média de plaquetas < 20.000 μ/L. Paciente com raros episódios hemorrágicos, mesmo com baixa contagem plaquetária. Perdeu seguimento por 2 anos, sem intercorrências no período. Ao retornar ao serviço, realizado mielograma com hiperplasia megacariocítica discreta, sem alterações morfológicas. Optado então, devido refratariedade por iniciar tratamento com Eltrombopague, com boa resposta clínica e níveis plaquetários dentro da normalidade. Alguns anos após retornar seguimento, pais foram redirecionados ao serviço com a irmã da paciente, de 9 anos, que também apresentava plaquetopenia identificada desde os 5 anos de idade, com contagem média de plaquetas < 100.000 μ/L e macroplaquetas. Tal fato, chamou atenção da equipe que realizou nova investigação de histórico familiar e obteve informação de que o pai e o avó das pacientes tinham histórico de plaquetopenia. Realizado hemograma do pai confirmando plaquetopenia. Devido a possível macrotrombocitopenia hereditária, optado por avaliação citológica de sangue periférico nos três familiares e identificado a presença de Corpos Döhle em neutrófilos, indicando o diagnóstico familiar de AMH. **Discussão:** A plaquetopenias apresentam, muitas vezes, um desafio diagnóstico e deve-se atentar para os diagnósticos diferenciais. Nos casos de macrotrombocitopenia, a AMH é diagnóstico diferencial considerável, elucidado pela citologia do sangue periférico, o que ratifica a importância desse exame na hematologia. Como exposto neste relato, na AMH, os pacientes em geral apresentam clínica hemorrágica frusta, muitas vezes incompatível com a contagem plaquetária, com sangramentos raros e leves. Isso acontece porque há um defeito na maturação e fragmentação megacariocítica, porém sem prejuízo à função plaquetária. Além disso, quando feita por contadores automatizados a contagem de plaquetas pode estar subestimada. A herança dominante, aponta para a importância da história familiar, entretanto e cerca de 30% apresentam mutação de novo. De forma geral, esses pacientes podem ser tratados apenas sob demanda com atifibrinoliticoe/ou transfusão de plaquetas. Há alguns casos na literatura semelhante ao relatado, com melhora da plaquetopenia com uso de Eltrombague. **Conclusão:** Apesar de rara, a AMH deve ser considerada no diagnóstico diferencial das macrotrombocitopenias. A suspeição e o diagnóstico precoce através da citologia do sangue periférico, são essenciais para evitar e reduzir o número de tratamentos inapropriados e consequentes riscos a esses pacientes.

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HEMOSTASIA E PAREDE VASCULAR: TROMBOSE

INTEGRATING PHENOMENOLOGICAL MODELING AND MACHINE LEARNING FOR PATIENT-SPECIFIC PREDICTION OF RECURRENT VENOUS THROMBOEMBOLISM

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Background: The prediction of Recurrent Venous Thromboembolism (RVTE) plays a crucial role in enhancing the prognosis of patients with coagulation disorders. In recent times, there has been a notable surge in studies focusing on developing scores based on machine learning models that utilize clinical data and blood counts as input. However, due to the inherent black-box nature of machine learning models, understanding the relationship between model features and the phenomenological aspects associated with blood clot formation and thrombosis has been challenging. To address this, incorporating mathematical modeling of blood coagulation alongside prediction techniques presents an alternative approach to improve both prediction accuracy and our understanding of the underlying phenomenological aspects. **Aims:** This study aimed to propose a patient-specific spatiotemporal phenomenological model for clot formation and utilize it to predict RVTE. **Methods:** A spatiotemporal model for blood clot formation was presented, encompassing convective, diffusive, reactive, and platelet aggregation effects. Blood flow was accurately modeled using Navier-Stokes equations, incorporating an additional term for flow resistance due to blood clot

formation. The model included quantitative variables from a complete blood count, enabling simulation personalized to each patient. The finite volume method was employed to solve the model within a clotting time of 10 minutes. The simulations involved 235 patients who had a thrombotic event, monitored by the State University of Campinas Blood Center, who underwent routine blood tests. Out of these patients, 49 were diagnosed with RVTE. Principal Components Analysis (PCA) and Partial Least Square (PLS) regression were utilized to identify the key variables influencing clot formation. These critical variables were then employed as inputs for an Artificial Neural Network (ANN) model, facilitating binary classification for RVTE prediction. **Results:** The patient-specific model demonstrated high sensitivity in distinguishing clot size variations between patients, with thrombus size directly related to platelet count in blood plasma. However, relying solely on clot size for RVTE prediction yielded low accuracy. To address this, the proposed strategy of using PCA and PLS to identify critical points in space and time successfully reduced the number of significant variables to 20. This reduction was essential in making the ANN training feasible, as the high dimensionality of the original dataset would otherwise result in excessive computational costs. The optimized ANN model achieved promising results: an Area Under Curve value of 81.51%, accuracy of 86.81%, and a true-positive ratio of 79.59%. **Discussion:** The findings suggest that incorporating phenomenological modeling based on blood test parameters can generate distinct clot formation profiles for individual patients, revealing differences in shape, growth time, and size. Dimensionality reduction techniques, such as PCA and PLS, effectively extract critical features, enabling the ANN-based model to achieve high accuracy in RVTE prediction. **Conclusions:** Integrating phenomenological modeling, machine learning, and statistical tools holds great promise for RVTE prediction. With further validation, this model could find application in clinical practice, providing valuable insights into blood clot modeling for patients at risk of RVTE.

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INTEGRATING CLINICAL AND BLOOD COUNT DATA INTO A HYBRID MODEL TO PREDICT THROMBIN PROFILES AND VENOUS THROMBOEMBOLISM RISK

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Background: Mathematical models play a crucial role in comprehending the intricate interactions and cascade reactions of chemical species involved in the blood coagulation cascade. Accurate models facilitate the prediction of thrombin profiles, aiding in diagnosing and prognosis diseases like Venous Thromboembolism (VTE). However, current mathematical models in the literature primarily rely on the concentration of chemical species and kinetic constants, overlooking essential variables such as age, sex, smoking, obesity, and diseases known as risk factors for thrombosis. **Aims:** The primary objective of this study is to develop a novel model where the kinetic parameters of the coagulation cascade are dependent on clinical and blood count data. This approach generate patient-specific thrombin profiles, considering well-known risk factors for thrombosis. **Methods:** A sensitivity analysis was performed on a coagulation cascade model based on a first-order differential equation system of 44 kinetic parameters. Critical kinetic parameters were allowed to vary between 30% and 300% of their default value. A hybrid Artificial Neural Network (ANN) model was employed to adjust these kinetic parameters, utilizing clinical and blood count data from 235 patients, of which 49 had thrombosis. The structure of the proposed hybrid model consists of an input layer using the clinical and blood count data of the patients, two intermediate layers, and a layer of prediction of the values of the critical kinetic parameters, which are used to calculate the thrombin profile from the mathematical model of the coagulation cascade. The ANN was optimized using a genetic algorithm to adjust weights and bias. The goal was to ensure that patients with thrombosis had a substantial area under the thrombin curve over time, while patients without thrombosis exhibited a lower area under the thrombin curve. **Results:** The analysis identified eight highly sensitive kinetic parameters related to factor V activation and thrombin-antithrombin III complex formation. These parameters were influenced by all input variables, especially age, sex, obesity, anticoagulant use, smoking, factor V Leiden, glucose, triglycerides, factor VIII, and G20210A mutation. The hybrid ANN model successfully predicted VTE recurrence with an accuracy of 98.72% and an Area Under Curve of 99.41%. **Discussion:** The findings of this model align with existing literature on the relationships between input variables, kinetic parameters, and thrombosis risk. The adopted approach allowed for the generation of patient-specific thrombin curves, which hold great potential for patient-specific models. The genetic algorithm proved efficient for optimizing the ANN hybrid model, achieving remarkable prediction accuracy. **Conclusions:** Machine learning techniques have demonstrated their capability to enhance models, especially in scenarios where the underlying processes are complex or not fully understood. Incorporating VTE risk factors into the cascade model enhances blood clotting models and improves their generality. This methodology could be employed with further validation to identify new therapeutic targets for VTE treatment.

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