CHIPS REGIMEN

Drug Information News Letter
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BRIDGING THE GAP A CLASS OF PROTEIN-CLEAVING ENZYMES SUSPECTED TO PLAY A ROLE IN HEREDITARY BRAIN DISEASE

Similar to Alzheimer's disease, the hereditary disease spinocerebellar ataxia type 17 (SCA17) leads to the destruction of brain nerve cells and the premature death of patients. The exact mechanisms of this disease are unknown, which is why there are no treatment approaches as yet. Researchers suspect that a class of protein-cleaving enzymes, so-called calpains, may play a role in the disease. By inactivating calpains, the researchers were able to halt the progression of the disease in a cell model.

Altered blueprint of a protein

Spinocerebellar ataxia type 17 (SCA17) is a rare, hereditary disease of the human brain. Due to the pathological alteration of a gene that contains the blueprint for a protein called TATA box binding protein (TBP), the protein is produced in cells in an abnormal conformation. As a result, its function is impaired.As a consequence, people affected by the disease develop symptoms starting in middle age, such as movement disorders, seizures, impaired mental performance as well as changes in character and behavior, which are associated with a degradation of tissues such as the cerebellum and brain stem.

Protein fragments are deposited

The molecular mechanisms that cause the disease are not yet fully understood. One mechanism that may contribute to or at least affect the disease is the cleavage of the disease protein TBP by certain enzymes. This cleavage leads to even more harmful fragments of the TBP protein in the nerve cells. "It is worth noting that previous studies have shown that these cleavage products also occur in the tissue of Alzheimer's patients.

Calcium balance is disturbed

A special class of protein-cleaving enzymes, i.e. calpains, can cause this cleavage of TBP. "In addition these enzymes are overactivated in cell and animal models of SCA17. Since calpain activity is calcium-dependent, this finding suggests that genes involved in controlling the calcium balance of cells may also be dysregulated.By inhibiting the enzymes through pharmacological or genetic approaches, reduction of the deposition of TBP

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and the production of the defective protein is done in a cell model. This applies to SCA17 as well as to similar neurodegenerative diseases, where it has already been demonstrated that calpains play a crucial role in the pathogenesis.

Weber, J.J., et al. (2022) Calpains as novel players in the molecular pathogenesis of spinocerebellar ataxia type 17. Cellular and Molecular Life Sciences. doi.org/10.1007/s00018-022-04274-6.

TODAYS WATCH

Vitamin D supplements show promise to counter the adverse effects of diabetes drug on bone health

Vitamin D supplementation may help offset damaging bone loss that occurs in some people who take canagliflozin, a commonly prescribed diabetes drug. SGLT2 inhibitors has been shown to slow the progression of diabetes-related kidney disease and is increasingly being considered as a first-line treatment option for people with diabetes who have a high risk for developing kidney and heart disease. However, some studies have found SGLT inhibitors to negatively affect bone health by accelerating loss of bone mineral density and hampering the activation of vitamin D by the body. The combination of these events can increase the risk of bone fracture. The volunteers some of whom were found to have preexisting low vitamin D levelstook canagliflozin, an SGLT2 inhibitor, for five days before and after they were given vitamin D supplements. People who were vitamin D-deficient, canagliflozin led to a significant decrease (31%) in the levels of a metabolite used to measure vitamin D levels, but a much smaller decrease (7%) in those with normal vitamin D status. The supplements then boosted levels of parathyroid hormone, which regulates calcium levels in the blood and vitamin D levels in the bones.

https://www.physiology.org/detail/news/2022/06/27/vitamin-d-supplements-may-offset-bone-loss-caused-by-diabetes-drug?SSO=Y

STUDENTS CORNER

Azithromycin Associated Risk of Ventricular Fibrillation

Azithromycin is indicated for thetreatment of various infectionsthat need IV therapy includingcommunity acquired pneumonia(CAP) and pelvic inflammatorydisease caused by susceptibleorganisms, including Legionellapneumophila. Azithromycin bindsto 50 S ribosomal subunit and23S rRNA and prevents protein-synthesis by inhibiting 50Sribosomal subunit. Ventricularfibrillation (VF) is an ineffectiveventricular contractions or fastshivering of the ventricular wallsthat prevents them from pumpingthe blood properly, which is a lifethreatening cardiac rhythm.SFDA has announced a safetysignal about risk of ventricularfibrillation associated with the useof Azithromycin. However, thispotential signal needs furtherinvestigation to confirm the risk,and healthcare professionalsshould be aware of this potentialadverse reaction.

• Safety Alerts, SFDA, 2022.(www.sfda.gov.sa)

CLINICAL CONNECTION:

Math model predicts several useful new drug combinations that may help treat heart attacks

Researchers used mice to develop a mathematical model of a myocardial infarction, popularly known as a heart attack.The new model predicts several useful new drug combinations that may one day help treat heart attacks. Typically caused by blockages in the coronary arteries, or the vessels that supply blood to the heart, these cardiovascular events are experienced by more than 800,000 Americans every year, and about 30% end up dying. But even for those who survive, the damage these attacks inflict on the muscles of the heart is permanent and can lead to dangerous inflammation in the affected areas of the heart.

Treatment to restore blood flow to these blocked passages of the heart often includes surgery and drugs, or what's known as reperfusion therapy. Mathematical algorithms were used to assess the efficacy of the drugs used to combat the potentially lethal inflammation many patients experience in the aftermath of an attack.

In medicine, differential equations are often used to monitor the growth of diseases in graph form.But this study chose to model how certain immune cells like myocytes, neutrophils and macrophages, cells imperative to fighting infection and combating necrosis (toxic injury to the heart), react to four different immunomodulatory drugs over a period of one month. These drugs are designed to suppress the immune system so that it doesn't cause as much damaging inflammation in parts of the heart that were damaged.This research focused on the drugs' efficacy an hour after the mice were treated.Their findings showed that certain combinations of these drug inhibitors were more efficient at reducing inflammation than others. This simulation is purely theoretical, it won't lead to improved therapies anytime soon. More precise mouse data is needed before their work can become an asset to other scientists.

Moise, N & Friedman, A., (2022) A mathematical model of immunomodulatory treatment in myocardial infarction. Journal of Theoretical Biology. doi.org/10.1016/j.

CASE DISSECTION

A Patient with Fever and Cough

A 71-year-old male was admitted because of fever and productive cough. He claims feeling okay until about 4d PTA when he noticed the onset of cough. Initially nonproductive, the cough began to become productive of yellowish sputum and was associated with left sided chest pain. Two days PTA he noticed feeling chills and had a temperature of 102oF. The fever, cough and chest pain continued over the next 48 hrs so he came to the General Medicine Department. He denied hemoptysis, weight loss, sore throat, sinusitis, back pain, diarrhea, rash, joint pain or headaches. He has a history of congestive heart failure related to ischemic heart disease that has been controlled with Lasix, and MetXL. He is a former smoker but quit 3 months ago when hiswife died of lung cancer. He denies alcohol use, recent travel, domestic pets or any risk factors. He is a retired lawyer and lives alone.

P.E. reveals a thin man in mild respiratory distress. T 102.4; R 28; P 120; BP 128/84; O2 saturation is 89% on room air. SKIN - normal but with decreased turgor; LN - none palp. HEENT - sinuses nontender; TMs mildly red but no middle ear fluid; oropharynx is mildly red but no exudate. CHEST - remarkable for splinting to the left side on deep inspiration + dullness to percussion ≈ 1/4 way up on left side; decreased breath sounds at left base, but egophony and bronchial breath sounds are evident as one listens more superiorly on the left side. The right chest is clear. COR - RRR without murmurs or rubs. ABD - soft, nontender without hepatosplenomegaly. NEURO - nonfocal.

LABS: Na 143, K 4.2, Cl 100, HCO3 29, Cr 1.0, glu 150 Hb 13.8, Hct 39.8, WBC 18.0 (54 segs, 5 bands, 41 lymphs), plts 255K

UA: clear/1.020/1+ protein/no cells or casts

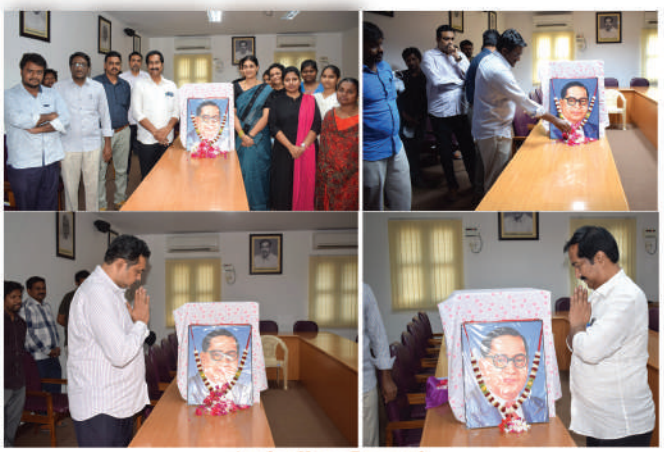
EKG: NSR/normal rate, intervals and no ischemic changes

CXR: nl heart size/left lower lobe infiltrate is present that obscures the left heart border

Sputum Gram's stain: a few PMN, many epithelial cells, and scattered Gram positive and Gram negative cocci and rods are seen.

QUESTIONS

1. What is your most likely diagnosis?
2. What host factors unique to this patient places him at risk for such a diagnosis?
3. What features of the history and physical exam support this diagnosis?
4. Describe the physical findings in the chest and what they indicate.
5. Is the sputum sample helpful in the diagnosis of this patient? What features of the Gram stain do you look for in evaluating the value of the sputum sample?
6. What kinds of infectious agents can produce this syndrome? Which would be most common?
7. Are there any other diagnostic tests you would order before initiating therapy?
8. What antibiotic(s) would you initiate in this patient empirically?
9. Should the patient be hospitalized or could he be treated as an outpatient? The patient's sputum culture grows normal flora. Blood cultures grow S. pneumonia that is susceptible to penicillin.
10. What would you do now, and how can we prevent this from recurring again?



Ambedkar Jayanti

World Earth Day

Two Day National Conference on Recent Advances in Pharmacotherapy

Freshers Day Celebrations

One Day Workshop on Clinical Pharmacy, Health Informatics and Leadership

Campus Recruitment Drive by Episource LLC

Pool Campus Walk-in for the position of Industry internship at Aurobindo Pharma Limited

International Day of Yoga 2022

Best Oral Presenter Award at International Postgraduate Conference on Pharmaceutical Sciences

We are Glad to Receive your Feedback to chipsregimen@gmail.com

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