BACKGROUND and OBJECTIVE: Rare diseases are congenital or acquired disorders that affects less than 1/2000 of the population. Almost all inherited metabolic diseases (IMD) are included in this definition which are sometimes difficult to diagnose. Multisystemic involvement, parental consanguinity and family history rise clinical suspicion of rare disorders. But they do not always have disease-specific signs and symptoms. Also, coexistence of multiple disorders complicates the clinical course of the patient. Occam's razor means patient’s symptomatology must be explained with single simplest etiology. It is a seven decades old philosophy, which suggests there is no need for more than one theory to explain a situation. Whereas, Hickam's dictum states patient's clinical findings may be secondary to two or more pathologies. Professor Hickam mentioned that a patient have as many diseases as he could have. In the era of precision medicine, it requires a continuous flow of hypotheses to diagnose a patient. In this presentation, we aim to highlight diagnostic odyssey of patients with multiple rare disorders.

Method: Retrospectively, medical records of patients with multiple rare diseases which are confirmed with genetic analysis were reviewed.

Patient-1: She is a 12-year-old with parental consanguinity who presented with profound hepatomegaly, hypoglycemia attacks since birth and also muscle wasting, hypertriglyceridemia, cardiomyopathy and myopathy with elevated creatine kinase in infancy. AGL gene analysis detected homozygous c.2270_2273delCATT pathogenic variant and she was diagnosed as having glycogen storage disease (GSD) type-3. On follow-up she developed periodical abdominal pain and arthritis. Molecular studies revealed p.E148V pathogenic variant on MEFV gene and her additional diagnosis was familial Mediterranean fever. With colchicine treatment, abdominal pain did not recur.

Patient-2: is a 3-month-old male who showed short stature, hepatomegaly, hypoglycemia, lactic acidosis, hypertriglyceridemia and hyperuricemia. Creatine kinase levels are normal. Glycogen storage gene panel detected a homozygous p.W77R pathogenic variant and he was diagnosed as having glycogen storage disease (GSD) type-1a. On follow-up he developed coarse facies, recurrent upper respiratory infections, intellectual development disorder, hirsutism and Mongolian spot. Urinary glycosaminoglycan electrophoresis showed increased excretion of heparane sulphate. α-N-acetylglucosaminidase level was 0.2 nmol/mL·hr (normal >15). NAGLU gene analysis detected homozygous p.W404* pathogenic variant and he was diagnosed as having mucopolysaccharidosis-IIIb. The patient died due to complications of both diseases.
Patient-3&4: They are brothers whose current ages are 19 and 18 years, respectively. They presented with hepatomegaly, hypoglycemia episodes, and myopathy. They have been diagnosed with GSD-3 in infancy with molecular studies which detected homozygous c.199C>T pathogenic variant on AGL gene. Occasionally, both had unexplained epistaxis in adolescence although they do not have chronic liver insufficiency. Coagulation studies detected prolonged partial thromboplastin time and low Factor-IX (1-5%) levels. Suspected diagnosis was Hemophilia-B. Genetic analysis of F9 gene revealed hemizygous p.R191C pathogenic variant which confirms the diagnosis.

Patient-5: is a 2-year-old female who had parental consanguinity, psychomotor retardation, microcephaly, and normal anion gap metabolic acidosis. She needed multiple hospitalizations for intravenous fluid resuscitation for metabolic acidosis. Renal function tests, serum electrolytes, basal metabolic investigations or neuroimaging revealed no abnormalities. WES detected homozygous c.287G>A pathogenic variant on WDR73 gene responsible for Galloway-Mowat Syndrome and homozygous c.232+1G>A pathogenic variant on CA2 gene responsible for carbonic anhydrase deficiency type-II. The patient is now on regular follow-up but did not develop any renal dysfunction or cerebral calcifications yet.

Patient-6: She was a 4-month-old female who was referred through newborn screening for suspected biotinidase deficiency. Her parents were consanguineous. She had 2 deceased siblings and they were floppy infants. Her biotinidase enzyme level was 2.8 (3.5–13.8) U/L and BTD gene analysis resulted with homozygous p.D444H pathogenic variant. Although she was properly treated with oral biotin, she developed unexplained hypotonia and respiratory insufficiency episodes without acute metabolic decompensation. Whole exome sequencing (WES) detected homozygous c.444G>A (p.W148*) pathogenic variant in COLQ gene which causes endplate acetylcholinesterase deficiency and she was diagnosed with congenital myasthenic syndrome type 5. Unfortunately, she died due to severe respiratory insufficiency after having pneumonia.

Patient-7: is a 9-year-old male who was diagnosed with biotinidase deficiency through newborn screening program. Biotinidase enzyme level was 2.3 (3.5–13.8) U/L and BTD gene analysis resulted with homozygous c.470G>A pathogenic variant. Biotin 5 mg/day was initiated. On follow-up, he had paleness after a febrile illness. Laboratory evaluation detected iron deficiency anemia and she was given 5 mg/kg/day oral iron preparation. Anemia persisted despite iron supplementation, glucose-6-phosphate dehydrogenase found to be decreased and additional diagnosis was glucose-6-phosphate dehydrogenase deficiency.

CONCLUSION: Collaborative effort is needed for diagnosis of patients with multiple rare diseases. Misdiagnosis, delayed diagnosis, moving from one clinician to another clinician, unnecessary tests and incorrect treatments are frequent. For some patients, the time from initial disease recognition or symptom onset to a final diagnosis takes years. These conditions often lack specific treatment but specific diagnosis enables genetic counseling for the family. Rather than the parsimony of a single condition explaining all the symptoms and signs, open-mindedness for possibility of multiple diagnoses and complex diagnostic methods such as WES or whole genome sequencing are helpful.