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Transitory pancreatic insufficiency in cystic fibrosis children

Dear Editor,

Pancreatic exocrine function is an important clinical marker for the severity of expression of cystic fibrosis (CF) and pancreatic insufficiency (PI) is one of the first manifestation of Cystic Fibrosis transmembrane conductance regulator (CFTR) protein dysfunction. It is present since the first months of life in almost all CF patients with two CF-causing mutations (functional classes I, II, III); conversely, the presence of a class IV or V mutation on at least one allele of the CFTR gene correlates with a pancreatic sufficiency (PS) phenotype in most cases [1,2].

The loss of pancreatic function generally appears during the first months and years of life and its early diagnosis allows the correct treatment avoiding malabsorption and malnutrition.

In order to prevent malabsorption and improve CF infants nutrition and growth, it is crucial to determine the pancreatic functional status since diagnosis. In clinical practice the best test to evaluate the exocrine function of the pancreas is pancreatic fecal elastase 1 (E1). The test is 93% sensitive and a 93% specific with a cut off of <200 µg/g of feces [3]. Normally E1 reaches adult levels in the first two weeks of life, thus this method is useful for screening PI/PS in CF infants with a positive newborn screening (NBS).

We report four CF infants with positive NBS in whom transient PI led to misclassification to “CF with PI”. Three infants have at least one CFTR gene mutation conferring residual function: F508del/2789+5G>A (two sisters), F508del/R1066H and the last is M1T homozygote.

2789+5G>A, c.2657+5G>A is a CF-causing variant located in intron 14 that may affect CFTR quantity with a residual function. In CFTR2 database, PI is reported in 40% of CF patients with this variant. 2789+5G>A is quite frequent in the Italian population (the fourth more frequent mutation), reported in 290 (5.4%) Italian CF patients [4]. Several studies demonstrated a milder phenotype in these patients. Data from the italian patient registry showed a very low percentage of PI (25.2%) in CF patients with this variant [5]. In some countries treatment with ivacaftor has been approved for individuals with this variant.

R1066H, pArg1066His, c.3197G>A, is a CF causing mutation. CFTR2 database reports PI in 31% of patients with F508del/R1066H genotype. This is a missense variant which may affect CFTR quantity and/or function. It is a rare variant, with an allelic frequency of 0,6% in the Italian population [4]. It was first described in a 20 years old PS CF patient; then it has been detected as a *de novo* mutation in an Italian subject diagnosed at 17 years of age with PS. Recently it has been identified together with the P5L variant in a child with a Pseudo Bartter Syndrome [6].

The patient with M1T homozygous genotype is a girl from Pakistani parents, she has been already described because affected also by Familial Exudative Viteoretinopathy [7]. The CFTR M1T, c.2T>C, p.Met1Thr, variant is located in exon 1 and it is suspected to prevent initiation of the translation. It is a rare mutation, allele frequency (0.8%) being reported only for patients from Bangalore and in Réunion Island population [8,9]. Only little information is available in CF Mutation Database, identified in three patients, two of which with PS.

In the first year of life, all our CF infants had E1 insufficient levels in several determinations, then they were labeled as PI and pancreatic enzyme replacement therapy (PERT) was quickly begun.

Monitoring pancreatic status during the follow-up, we assisted to a spontaneous raise of E1 levels, that reached stably values above 200 µg/g at respectively 2, 4, 5 and 6 years of life (see Fig. 1) allowing us to stop PERT. All patients maintained normal weight growth. They were re-classified as “CF with PS”.

CFTR genotype may predict pancreatic exocrine function, as the presence of at least one CFTR mutation of functional class IV or V generally correlate with PS, but there is a clinical variability determining fluctuation of E1 values. We reported four CF infants initially labelled as PI, in whom during the follow-up a spontaneous raise of E1 values reached PS value as expected from their genotypes. Monitoring regularly pancreatic status also in PI children with CFTR mutations with a residual function is pivotal to avoid unnecessary PERT.

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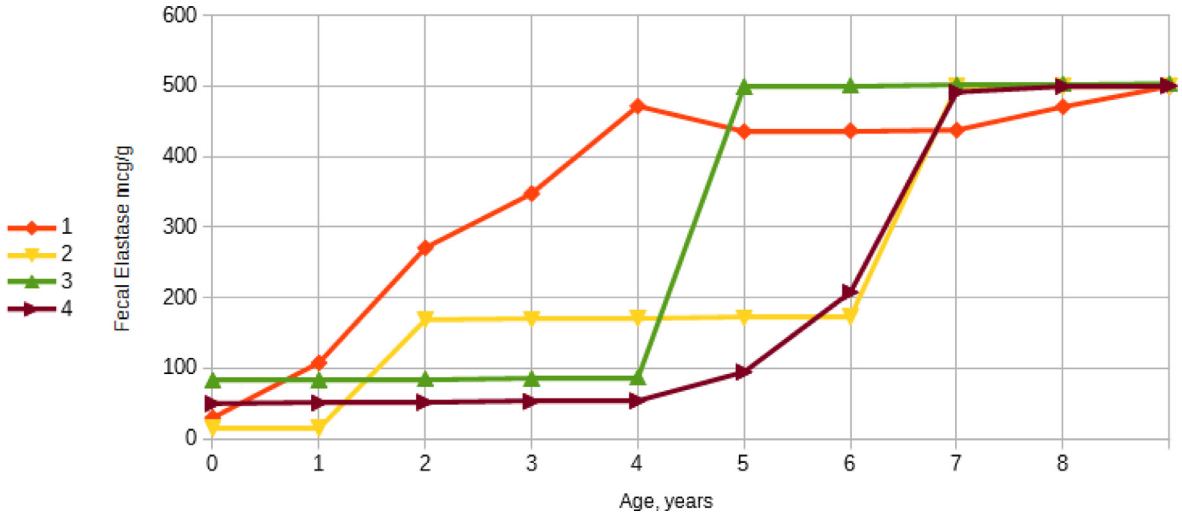

Fig. 1. Trend of Fecal Elastase 1 in first years of life.

Declaration of Competing Interest

The authors declare that there are no conflict of interests.

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