No Evidence to Support a Bimodal Age of Onset in Idiopathic Chronic Pancreatitis

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(Main text, maximal 750 words)

Dear Editor,

We read with interest the article by Lewis and colleagues.[1] Their main aim was to use the North American Pancreatitis Study 2 cohort to reexamine the findings of Layer *et al*. who, back in 1994,[2] reported a bimodal age of onset in idiopathic chronic pancreatitis (ICP), discriminating between early-onset (EO-ICP; <35 years) and late-onset (LO-ICP; >35 years) forms of ICP. Lewis and colleagues claimed that the age of onset of pancreatitis symptoms in their 130 ICP patients followed a bimodal distribution that was nearly identical to the Layer findings. However, their data (see Figure 2A,B in Lewis *et al*.[1]) actually exhibit a rather uniform distribution. In this regard, it is pertinent to mention that the original Layer findings, based upon an analysis of only 66 subjects, were recently challenged by Liu and colleagues from three standpoints.[3] Firstly, formal statistical analyses of the reconstructed Layer data revealed that the age of onset in ICP was uniformly distributed. Secondly, a "bimodal" age distribution was never actually formally demonstrated in any subsequent study. Thirdly, the age at onset in 1633 Chinese ICP patients (the largest cohort reported to date) displayed an approximately normal distribution. Therefore, to date, there are no studies that provide convincing evidence to support a bimodal age of onset in ICP.

The above notwithstanding, we believe that the classification of ICP patients as EO-ICP and LO-ICP, using an age of onset at 35 years as the cut-off value, may nevertheless still be usefully maintained for the following reasons. First and foremost, ever since the Layer study, age of onset at 35 has been frequently used to draw an arbitrary distinction between EO-ICP and LO-ICP, even though the original description of a "bimodal" distribution of age at onset of ICP was incorrect. Secondly, age of onset at 35 years does not differ much from the median age at onset of ICP, at least in the context of the two latest studies.[1,3] Indeed, the median age at onset for the 1633 Chinese ICP patients was 38.2 years.[3] The precise corresponding value

from the Lewis study is unclear; however, survey of the original data (see Figure 2A,B in Lewis *et al.*[1]) indicates that the median age at onset should be somewhere between 35 and 40 years. Thus, age of onset at 35 should separate ICP patients into two roughly equal groups. Thirdly, there are significant clinical differences between the EO-ICP and LO-ICP patients thus defined.[1-3] Lastly, there are also significant differences with respect to genetic susceptibility between EO-ICP and LO-ICP patients, as evidenced by the Lewis study;[1] for example, EO-ICP patients exhibited a much higher detection rate of pathogenic *SPINK1*, *CFTR* or *CTRC* variants as compared to LO-ICP patients (49% vs 23%).

In addition to the analysis of 61 EO-ICP patients and 69 LO-ICP patients, Lewis and colleagues also studied 308 light-to-moderate alcohol drinkers with chronic pancreatitis and 225 patients with alcoholic chronic pancreatitis (ACP). Three findings were noteworthy. Firstly, as distinct from the ICP patients, the distribution of age at onset of pancreatitis in both of the two latter cohorts approximates to a normal distribution (see Figure 2C,D in Lewis *et al.*[1]), implying qualitatively different pathological mechanisms between ICP and ACP. Secondly, pathogenic *SPINK1*, *CFTR* or *CTRC* variants were found in a significant fraction of light-to-moderate alcohol drinkers with chronic pancreatitis (26%) and ACP patients (23%), although the corresponding detection rate in ICP patients (EO-ICP and LO-ICP combined) was rather higher (35%). Thirdly, some pathogenic variants were found to significantly accelerate the onset of pancreatitis in EO-ICO patients and/or in light-to-moderate alcohol drinkers with chronic pancreatitis. With regard to the two latter points, it should be noted that a recent large Chinese study reported that pathogenic genotypes involving the *SPINK1*, *PRSS1*, *CTRC* and/or *CFTR* genes were present in 57.1%, 39.8%, and 32.1% of the ICP, ACP and smoking-associated chronic pancreatitis patients, respectively, and influenced age at disease onset and clinical outcomes in all subgroups.[4] Despite some differences in terms of the ICP and ACP definitions employed as well as ethnic differences between the studied

cohorts,[1,4] these findings serve to emphasize the key role of genetic risk factors in the etiology of both ICP and ACP. However, unlike the case of the rs10273639-tagging common *PRSS1-PRSS2* haplotype,[5,6] a gene-environment interaction between these rare pathogenic variants and alcohol consumption was not immediately evident because of their lower detection rate in ACP as compared to ICP.

Finally, it would have been helpful if details of the pathogenic *SPINK1, CFTR* or *CTRC* variants[1] had been made available.

References

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