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Novel diagnostic parameters for AADC deficiency in general metabolic urine screening

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Introduction

Aromatic L-amino acid decarboxylase (AADC) deficiency in most cases is a treatable defect in the biosynthesis of the biogenic amine neurotransmitters dopamine and serotonin. Patients are usually detected in infancy due to developmental delay, hypotonia and extrapyramidal movements, but the clinical presentation is variable and can initially be quite mild and/or aspecific. Until now the only way to detect this disorder in general metabolic screening of urine was to identify vanillactic acid (VLA) in GC-MS analysis of organic acids (see figure 1A). Because of the sometimes only small increase of VLA, and/or insufficient analytical sensitivity, AADC deficiency is probably seriously underdiagnosed. We present new findings in recently diagnosed patients that have yielded promising additional diagnostic parameters.

Cases

The first case (HC) is a boy with hypotonia, hypoglycemia and metabolic acidosis, detected at 13 days of age, by organic acids analysis of urine. The second and third cases are two brothers (AR, PR) both with dystonia, and oculogyric crises in one, detected at ages of 6 and 10 years respectively, in whom the diagnosis had been missed by two laboratories in organic acids analysis of urine, but eventually established in our laboratory by the finding of elevated urinary L-DOPA and/or dopamine. All 3 cases were confirmed by CSF neurotransmitter metabolites and plasma AADC activity measurements (see table 1).

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Methods

GC-MS of organic acids after ethoximation, HPLC-ECD of L-DOPA and dopamine.

Results

In the first case the urinary OA profile (figure 1B) not only showed elevated VLA, but also vanilpyruvic acid (VPA), N-acetylvanilalanine and N-acetyltyrosine. The brothers AR and PR appeared to have hyperdopaminuria and/or clearly elevated L-DOPA (see table 1).

Discussion

AADC deficiency in the neonatal case HC was unexpected because of the unspecific clinical symptoms and was only revealed by careful inspection of the GC-MS profile of the urine (1). The presence of the 3 newly recognized compounds is very likely to be characteristic for the defect, as they can be explained to be alternative metabolites of the accumulating AADC substrate: DOPA. The acetylated products are probably formed by aspecific acetylation as is also seen in other metabolic defects, eg. N-acetyltyrosine in tyrosinemia. Detection of the compounds relies on high-standard GC-MS. Because of the relatively small peaks of the compounds of interest, the optimal strategy is to use a special program for automatic MS library search of these metabolites. The dopaminuria, which seems to be contradictory in AADC deficiency,

Table 1. CSF and urinary biogenic amine metabolites and plasma AADC activities of the AADC deficient patients HC, AR and PR

	HC	Ref. Range	AR	Ref. Range	PR	Ref. Range
CSF (nmol/L)						
HVA	83	302 - 845	38	148 - 434	56	137 - 582
5-HIAA	<5	152 - 462	17	68 - 115	17	68 - 220
MHPG	<5	51 - 112	<10	28 - 60	<10	39 - 73
VA	1200	<50	494	<50	605	<50
Urine (nmol/mmol creat)						
DOPA	9440	64 - 336	3998	7 - 62	4714	5 - 108
Dopamine	2426	179 - 1541	1211	41 - 487	455	263 - 542
Plasma (U/L)						
AADC	< 1	36-129	<10	18 - 43	<10	18 - 43

because dopamine can not be synthesized, was already described earlier (2), as well as the urinary accumulation of DOPA, but the paradoxal dopaminuria now also appears to have diagnostic value.

Conclusion

The cases we present clearly demonstrate the additional value of the newly discovered diagnostic parameters vanilpyruvic acid (VPA), N-acetylvanilalanine and N-acetyltyrosine. This provides new chances for detection of AADC deficiency.

References

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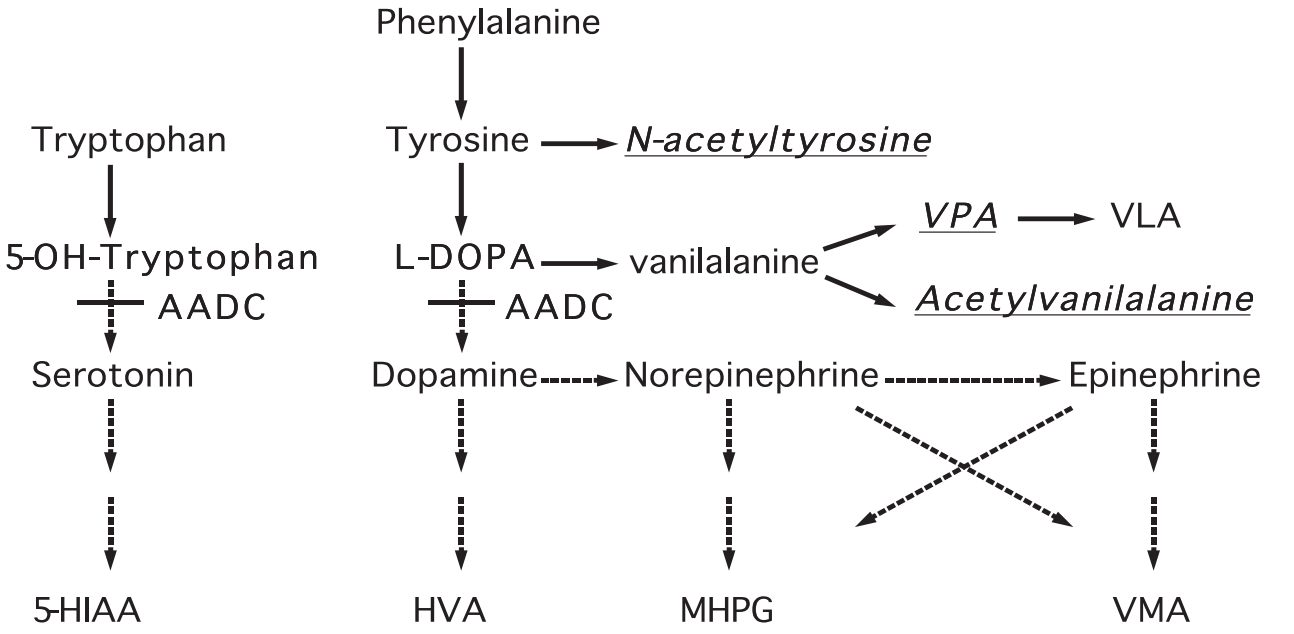

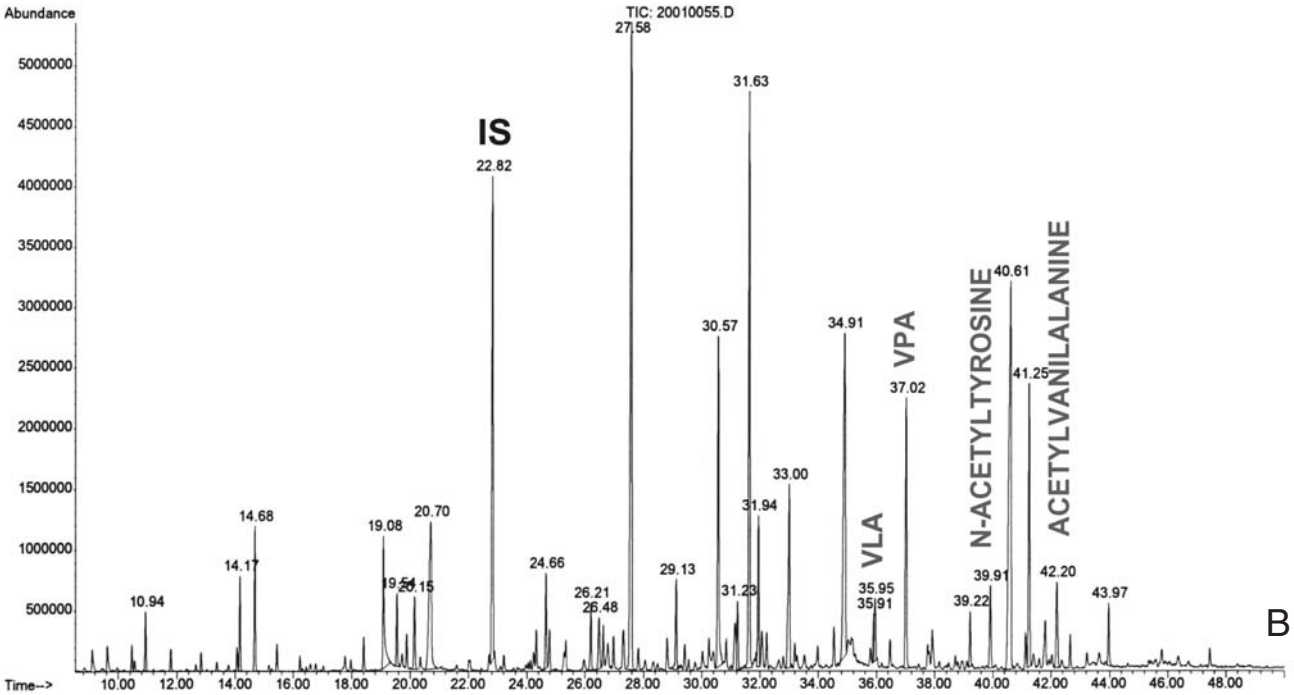

Figure 1. The 3 novel metabolites N-acetyltyrosine, vanilpyruvic acid and acetylvanilalanine in AADC deficiency in the metabolic pathway (A) and their positions in the organic acid profile of the urine of a patient (B).