

COI: Nothing to be disclosed

## Introduction

## Materials and Methods

## Conclusions

1) These results suggest the possibility that GABAergic interneurons in auditory networks (pathway) play an important role in AH.

2) The treatment by small dose of sVPA showed successful effects, for AH in ASD .

**This treatment has a value to be tried.**

|       |                |                                                                                                                                                        |                                                |                                             | Mean                     | 4.91                                                                                                                                    | 6.81                            | 7.96                                         | 3.29                                            | 2.44                                                     |                     |
|-------|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|---------------------------------------------|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|----------------------------------------------|-------------------------------------------------|----------------------------------------------------------|---------------------|
|       |                |                                                                                                                                                        |                                                |                                             | Maximum                  | 9.05                                                                                                                                    | 8.93                            | 10.00                                        | 7.07                                            | 5.52                                                     |                     |
|       |                |                                                                                                                                                        |                                                |                                             | Minimum                  | 2.79                                                                                                                                    | 4.85                            | 6.25                                         | 0.75                                            | 0.68                                                     |                     |
|       |                |                                                                                                                                                        |                                                |                                             |                          | TypeA<br>(20Cases/20)                                                                                                                   | TypeB<br>(14Cases/20)           | TypeC<br>(12Cases/20)                        | VPA medication                                  |                                                          |                     |
| Cases | Age<br>(years) | Triggers of AH                                                                                                                                         | Sharp,<br>screaming or<br>highpitched<br>sound | Dissonant<br>and<br>reverberating<br>sounds | High amplitude<br>sounds | Age to start<br>VPA                                                                                                                     | Initial<br>dose(mg/kg<br>g/day) | Maintenance<br>dose of<br>VPA<br>(mg/kg/day) | Time to<br>appearance of<br>effects<br>(months) | Observation<br>Period after<br>VPA medication<br>(years) | Efficacy            |
| M1    | 4.00           | Vacuum cleaner, hair dryer, baby crying                                                                                                                | 1                                              |                                             | 1                        | 2.90                                                                                                                                    | 7.03                            | 8.59                                         | 2.47                                            | 1.11                                                     | Effective           |
| M2    | 4.97           | Vacuum cleaner, toilet flush sound                                                                                                                     | 1                                              | 1                                           |                          | 3.14                                                                                                                                    | 6.90                            | 6.90                                         | 4.30                                            | 1.83                                                     | Effective           |
| M3    | 5.86           | Vacuum cleaner, hair dryer, children's screams, reverberation of speakers in gymnasium                                                                 | 1                                              | 1                                           | 1                        | 3.77                                                                                                                                    | 7.95                            | 7.95                                         | 2.90                                            | 2.08                                                     | Partially effective |
| M4    | 5.86           | Vacuum cleaners, hair dryers, toilet flush sounds, Construction noise, interphon noises, noises outside the house, Hymns and Christmas songs in church | 1                                              | 1                                           | 1                        | 3.32                                                                                                                                    | 8.28                            | 8.28                                         | 1.87                                            | 2.54                                                     | Effective           |
| M5    | 6.50           | Sounds of bells sound like thunder → disappeared, and became able to attend in church                                                                  | 1                                              |                                             | 1                        | 4.72                                                                                                                                    | 7.27                            | 7.27                                         | 1.83                                            | 1.79                                                     | Effective           |
| M6    | 7.01           | Sudden loud noises, the sounds in Disneyland, the rubbing noises of supermarket vinyl                                                                  | 1                                              | 1                                           |                          | 5.03                                                                                                                                    | 7.89                            | 7.89                                         | 2.70                                            | 1.98                                                     | Effective           |
| M7    | 7.67           | Air towels, the echoes of a concert hall, the squeak of buggy                                                                                          |                                                | 1                                           | 1                        | 4.71                                                                                                                                    | 7.27                            | 9.09                                         | 2.00                                            | 2.96                                                     | Effective           |
| M8    | 8.30           | Noises of vacuum cleaners, hairdryers, Loud noises in theaters                                                                                         | 1                                              | 1                                           |                          | 5.50                                                                                                                                    | 7.50                            | 9.66                                         | 0.25                                            | 2.79                                                     | Effective           |
| M9    | 8.33           | The sound of cash registers, children's voices, and the reverberation at swimming pools                                                                |                                                |                                             |                          | 4.61                                                                                                                                    | 7.50                            | 10.00                                        | 20.67                                           | 3.73                                                     | Effective           |
| M10   | 8.66           | Air towel, puff-puff sound of air pump.                                                                                                                |                                                |                                             |                          | 5.05                                                                                                                                    | 4.85                            | 9.09                                         | 2.30                                            | 3.62                                                     | Effective           |
| M11   | 9.29           | Speaker sound at athletic events                                                                                                                       | 1                                              |                                             | 1                        | 5.38                                                                                                                                    | 5.21                            | 7.81                                         | 4.80                                            | 3.91                                                     | Effective           |
| F1    | 6.24           | Train announcements, departure bells, vacuum cleaners, air towels                                                                                      | 1                                              | 1                                           | 1                        | 2.79                                                                                                                                    | 6.49                            | 6.49                                         | 2.33                                            | 3.45                                                     | Effective           |
| F2    | 6.31           | Noises in classroom, flushing toilets.                                                                                                                 | 1                                              | 1                                           |                          | 5.62                                                                                                                                    | 8.93                            | 8.93                                         | 4.83                                            | 0.68                                                     | Effective           |
| F3    | 6.55           | Noises of vacuum cleaners, air towels, flushing toilet                                                                                                 | 1                                              | 1                                           |                          | 4.73                                                                                                                                    | 7.27                            | 7.27                                         | 1.87                                            | 1.82                                                     | Effective           |
| F4    | 7.26           | Vacuum cleaners, sound of warm-air fan in toilet                                                                                                       | 1                                              | 1                                           |                          | 5.34                                                                                                                                    | 6.70                            | 6.70                                         | 2.33                                            | 1.92                                                     | Effective           |
| F5    | 8.16           | Sounds of 1)Vacuum cleaner, 2)Air towel, 3) Siren of an ambulance or fire-engine, 4) Baby cry                                                          |                                                |                                             | 1                        | 4.71                                                                                                                                    | 6.25                            | 6.25                                         | 2.33                                            | 3.45                                                     | Partially effective |
| F6    | 9.55           | Noises in a crowd, Air towel, Creaking sound of a train, Speaker sound                                                                                 | 1                                              | 1                                           | 1                        | 4.92                                                                                                                                    | 6.67                            | 8.33                                         | 2.23                                            | 4.63                                                     | Effective           |
| F7    | 11.28          | The sound of siren, telephone, television and radio.                                                                                                   |                                                |                                             | 1                        | 5.76                                                                                                                                    | 5.92                            | 7.69                                         | 0.77                                            | 5.52                                                     | Effective           |
| F8    | 13.20          | Flushing toilets, microwave dings, vacuum cleaners, hair dryers, air towels, barking dogs, platform noises                                             |                                                |                                             | 1                        | 7.17                                                                                                                                    | 5.10                            | 7.50                                         | 1.07                                            | 1.24                                                     | Effective           |
| F9    | 14.85          | The sound of drums, the ding of a microwave oven, the sound of a television, the gutter-patter of rainfall, and the echoes in a studio                 | 1                                              | 1                                           | 1                        | 9.05                                                                                                                                    | 5.17                            | 7.58                                         | 1.97                                            | 1.75                                                     | Partially effective |
|       |                |                                                                                                                                                        | 1=Yes                                          |                                             |                          | Effective=AH symptoms completely or sufficiently disappeared<br>Partially effective=AH symptoms partially or insufficiently disappeared |                                 |                                              |                                                 |                                                          |                     |

○ The materials were **20 children** (11males, 9 females) of ASD (autism spectrum disorder) with severe AH(auditory hypersensitivity) from the age of **4.0 to 14 years**.

○The AH triggers were divided into three types (Type A for Sharp and high-pitched sound, Type B for Disharmonic and reverberating sounds and Type C for High amplitude sounds) and the effect of sVPA was evaluated for each types each children.

**At first as emotional stabilizer, but not effective for AH.**

**3 cases took sVPA(sustained-release valproic acid) as the initial treatment for AH.**

**1 case took both initially.**

● For safety considerations, we decided the dose of VPA used 1/4 - 1/2 of the minimum standard dose of 20 (-40) mg/kg/day used for antiepileptic drugs, i.e. 5 – 10 mg/kg/day.

**OA sustained-release type VPA** was used to stabilize blood levels.

○The age to start sVPA was from 2.79 to 9.05 (mean 4.91) years of age.

- sVPA was **finally** used with the dose of **6.25 to 10.0 mg/kg/day**.

We report here our experience to treat AH in ASD children by a small dose of **sustained-release valproic acid (VPA)**.

## Results

**1) In all cases, all trigger types of AH phenomena (type A,B,C) became milder (3 cases) or disappeared (17 cases).**

**5 cases who daily suffered from flushing sound in a lavatory became free.**

The monthly panic in a case triggered by siren of ambulance etc. disappeared within a month at the level of once a year after the treatment.

2) The dose of sVPA found to be effective ranged from 6.25-10 mg/kg/day, with a mean of 7.96 mg/kg/day, and the time required for efficacy was within 5 months in 19 cases, with a mean of 3.29 months, except for one case with 20.67 months.

## REFERENCES

1)Mastsuzaki J et al.Progressively increased M50 responses to repeated sounds in autism spectrum disorder with auditory hypersensitivity: a magnetoencephalographic study, PLoS One. 2014 Jul 23;9(7).

2)Cellot1 G, Cherubini E.GABAergic Signaling as Therapeutic Target for Autism Spectrum Disorders,Front Pediatr., 2014 Jul 8:2:70