Outstretched Index Finger - A Pointer is Peculiar Behaviour Characteristic of Angelman Syndrome in Adults – A Case Series Study

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Abstract: Objective: To describe a behavioural feature, the outstretched pointing (and shaking) index finger, as a clue to the clinical diagnosis of Angelman syndrome (AS) in adults.

Methods: A case series, consisting of 43 adult individuals with the clinical diagnosis of AS, approved by genetic testing is presented. In 16/43 patients the clinical diagnosis was made by the author, mostly due to behavioural signs, including the pointing gesture, which he had increasingly noticed as a behavioural key feature in his adult patients with AS.

Conclusion: Pointing with the outstretched index finger is a communicative gesture frequently seen in adult persons with AS. Its absence is most likely due to more limited motor and/or intellectual functions, in phenotypes caused by deletions of 15q11-13 respectively. It can be seen as a clinical sign that significantly contributes to the diagnosis in adulthood.

Keywords: Angelman syndrome, behavioural phenotype, index finger.

INTRODUCTION

Angelman syndrome (AS) is a neurogenetic disorder with an incidence of 1 in 12 000 – 20 000 births [1]. Harry Angelman [2] stated in his first report on three children affected by that syndrome: “their flat heads, jerky movements, protruding tongues and bouts of laughter give them a superficial resemblance to puppets,…, which may provide for easy identification”.

The updated consensus for diagnostic criteria of AS mentions tremulous movement of limbs, frequent laughter/smiling, apparent happy demeanor, easily excitable personality, often with hand-flapping, or waving movements, hypermotoric behavior, and speech impairment as consistent symptoms as well as protruding tongue, excessive chewing/mouthing behaviours and uplifted, flexed arm position especially during ambulation as associated symptoms [3].

AS is caused by heterogeneous molecular defects involving the AS critical region of chromosome 15 (15q11-13), either by maternally derived deletion (65-75% of AS cases), UBE3A-point mutations/small deletions within this gene (5-11%), paternal uniparental disomy of chromosome 15 (3-7%) or by imprinting defects (3%) [4].

In their article on the clinical profile of AS at different ages, Buntinx and coworkers note that diagnosing AS in older individuals may be complicated because they tend to calm with increasing age [5]. This might result in difficulties to recognize the behavioural phenotype that is certainly crucial if one aims to grasp the gestalt of this syndrome in a clinical setting.

With this short contribution, we wish to hint at a behavioural sign that, together with other symptoms, may serve as an element constituting the clinician`s engram of AS.

PATIENTS AND METHODS

In our outpatient service for adults with severe intellectual and developmental disabilities, we have treated 43 patients (27 male, 16 female) with the clinical and molecular genetic diagnosis of AS between 2005 and 2018. Their age ranged from 20 to 68 years (mean±SD, 36.9±6.1years).

All patients were clinically diagnosed with AS and genetic testing was done in each of them. Methylation-Specific Multiplex Ligation-dependent Probe Amplification (MS-MLPA) or Methylation-Specific Polymerase Chain Reaction (MS-PCR) Tests were performed as well as *UBE3A*- sequencing in a second diagnostic step. In patients who had been tested in earlier years, the genetic report merely described “Angelman typical methylation pattern” or a “loss of maternal methylation” that was not further specified.

In 16 patients the clinical diagnosis of AS was first made in our clinic. One of them, a 55 years old female patient came with the diagnosis of Down syndrome.

The communication behaviour of patients was observed during the outpatient examination and was

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videotaped in several patients. In cases in which initial examinations in our centre went back longer, caregivers were asked for the current communication habits of the patient concerned ("how would the patient call your attention to something?") during the last previous examination or in the context of a telephone conversation.

Data had been collected primarily in a systematic retrospective manner. Legal guardians granted their permission to publish photos of the patients they cared for.

RESULTS

Genetic testing revealed a loss of maternal methylation (not otherwise specified) in 13 patients, deletions of the AS critical region in 14, *UBE3A*-mutations in 8, uniparental disomy in 5, and an imprinting defect in two further patients with AS.

In 34 out of 43 patients with AS we unequivocally identified that pointing with the index finger was their (one of their) habitual mode(s) to communicate, to make others aware of something (Figure **1**). In most of the cases, arm and hand were outstretched, with significant crude shaking movements of the extremity, due to a coarse tremor affecting these persons. A simultaneous iterative vocalization (e.g. "ma, ma, ma…." or "da, da, da…") could be perceived in many patients. Sometimes both arms/hands were outstretched with bilateral pointing (Figure **2**).

Figure 1: 27 years old man with AS intending to draw attention to a person who has disappeared behind a door.

(Consent to the publication of the photo was given by the guardian).

Figure 2: 37 years old man with AS making contact by pointing with the index finger of either hand.

(Consent to the publication of the photo was given by the guardian).

In three cases flailing movements of the outstretched (and shaking) upper limb, with all fingers bound forward, were seen in corresponding situations and two further patients would have performed snatching hand movements likewise. Three individuals did not exhibit any communicatively motivated hand movements at all. Two of the latter had a severe motor impairment, without any capacity of assisted walking or standing.

In five of eight cases with no clear cut "extended index finger sign" deletion of the Angelman critical region was detected, a loss of maternal methylation, not otherwise specified and uniparental disomy in one other case. In three of the six cases with deletions but without a clear cut "extended index finger sign" habitual goal-directed, grasping hand movements had been described.

Table **1** shows molecular genetic findings and distribution of the "extended index finger" feature.

DISCUSSION

Over time we had become aware of this particular aspect, namely the outstretched index finger, as a consistent behavioural sign of our AS-patients, which was conveyed in communicative situations.

By far most of our adult AS-patients pointed a finger at something or someone in considerable frequency, to make their environment aware. Through an interference of that communicative gesture with tremulous hand-/arm-movements, it became a "shaking finger" in many of the cases. Probably this "shaking

Table 1: Distribution of AS Genetic Subtypes and Finding of an Outstretched Index Finger

Genetic subtype	number of AS patients	number of AS patients with an "outstretched index finger sign"
15q 11-12 deletion	14	9
UBE3A- mutation	8	8
imprinting defect	3	3
uniparental disomy (UPD)	5	4
loss of maternal methylation not otherwise specified	13	11

finger" took the role of an important hint in those 16 patients in which AS had not been diagnosed until then. It contributed considerably to what we described as the gestalt of AS and, accordingly, to the final diagnosis.

Since we studied persons from Europe only, it cannot be ruled out that the communicative gesture described is a culture-specific phenomenon.

In six out of nine persons without an unequivocal "index finger sign" deletion of the Angelman critical region could be detected. Their level of motor and coordinative abilities, as well as cognitive development, was markedly below that of the other persons with AS included in this evaluation.

The findings of an index finger are based solely on the observation by the author. So they have not been raised by independent observers. Due to the unambiguousness of the gesture, a high level of interrater reliability should also be assumed in the case of several independent observers and therefore the evaluation of findings by one clinical observer is most likely very valid.

Special movements and gestures can be a typical sign in some syndromes (e.g. patients with Smith-Magenis syndrome hug themselves)[6]

As far as the author is aware, the "shaking index finger" does not occur in any other syndrome associated with an intellectual and developmental disability (IDD).

We dare to interpret these consistent findings as an affirmation of the strong communicative impetus of most persons with AS. This may seem to some extent contrary to several studies that found a co-morbid diagnosis of AS and autism/autism spectrum disorders in 50 to 80% of the investigated individuals [7-10]. In the study performed by Bonati and coworkers applying the autism diagnostic observation schedule (ADOS) the comparison of individuals with AS and autistic disorder and individuals with idiopathic autism revealed differences between both groups especially in the items referring to the reciprocal social interaction domain, including "pointing"[7]. Not only in study groups with AS but also with other genetically determined developmental disabilities, subjects with communication difficulties may, however, have had an overrated autism diagnosis [11]. Beyond that, recent studies revealed that the ADOS as such should no longer be considered the gold standard in autism diagnosis – especially in persons with genetically determined developmental disabilities - as "the accuracy of the coding depends on the experience of the coder with the ADOS as well as on characteristics of the cases and the quality of its administration" [12]. Its discriminative values (and the discriminative values of other commonly used autism diagnostic instruments) seem to be "substantially affected by individual characteristics beyond ASD symptoms". The latter seems to be of particular importance to people with intellectual disabilities and for individuals with elevated emotional/behavioural problems [13]. The outstretched index finger in individuals with AS may be seen as a pointer to the ability to reciprocal contact and communication rather than as a stereotypic (autistic) behaviour, for which it can mistakenly be held.

CONCLUSION

Many cases of AS are not yet correctly diagnosed in adulthood. An unerring clinical diagnosis depends substantially from the experience and intuition of the clinician. The latter gets certainly promoted by the morphological and behavioural gestalt which the physician holds for reference. This should contain features easy to grasp, common in a given syndrome and less frequent in others, i.e. features of high sensitivity and specificity. This seems, at least in part, to be true for the outstretched (and shaking) index

finger in individuals with AS, as far as one can deduce this from clinical observation. Furthermore, this behavioural symptom emphasizes the pronounced communication pleasure of adults with AS and may be considered as an additional negative argument in the debate as to whether AS is truly associated with ASD [14].

CONFLICT OF INTEREST

The author declares no conflict of interest. I confirm that I have read the Journal`s position on issues involved in ethical publication and confirm that this report is consistent with those guidelines.

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