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The Rare Kabuki Syndrome in Greece: Case Study

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Abstract

There are some genetic syndromes of intellectual disability that are not particularly well-known, even among Special Education teachers, who find it hard to distinguish them. This difficulty is related to the infrequency of these syndromes. The present study focuses on one of these syndromes, the "Kabuki syndrome", and attempts to illustrate various aspects of it. The triggering event for this study was the researchers' contact with an 8-year-old student in a Greek school that was diagnosed with Kabuki syndrome.

Keyword: Kabuki syndrome

1. Origin of the syndrome's name

"Kabuki", in Japanese, is a kind of traditional theatre, with its roots back to the 17th century AD in the ancient capital Kyoto. Although created by a woman (Okuni), it was soon forbidden for women to participate in theatre. Women actresses often worked as prostitutes when not on stage and the government thought that the public morals would be protected by this ban. As a result, men also took the women's roles - "onnagata" (Mhanni & Chudley, 1999). This ban led to the very special make-up of the kabuki actors. It includes wax application on eyebrows and oil coating on face, so that the make-up "sticks". The eyebrows constitute one of the most important aspects of depicting and expressing a role.

2. Locating the syndrome

The syndrome was first described in Japan in 1981, by two scientists working separately in two different places, Dr. Niikawa in Kanto and Dr. Kuroki in Hokkaido. In 1969, Norio Niikawa (geneticist) finds a boy with intellectual disability and particular face characteristics and other anomalies. Not having seen anything similar before, he wondered whether this was a disorder never diagnosed before. In the years that followed, he met more people with the same face characteristics, so, in 1979, he presented his findings and suggestions at the first dysmorphology conference that was held in Japan. Similarly, Kuroki, who also participated in the same conference, identifies these symptoms and realizes that he had also noticed similar cases. In 1981, the two scientists presented separate articles with their observations, referring to the syndrome (Kasdon & Fox, 2012).

Niikawa connects these people's look with the appearance of the "Kabuki" traditional Japanese theatre actors, so the syndrome got the name "Kabuki make-up syndrome". More particularly, the arched eyebrows, thick eyelashes and large palpebral fissures that the people described by Niikawa had, reflected the "Kabuki" actors' mask. However, in today's literature this syndrome is referred to as "Niikawa-Kuroki syndrome" and "Kabuki syndrome" (Kasdon & Fox, 2012), since the "make-up" term is considered disdainful against people suffering from this syndrome (Mhanni & Chudley, 1999). Kabuki syndrome, is a rare syndrome connected with intellectual disability and occurs in 1 every 32,000 births in Japan (Sanz, Lipkin, Rosenbaum & Mahone, 2010). Since the syndrome was first located and studied in Japan, it was considered to regard the Japanese population only.

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However, an increasing number of people with this syndrome is noticed today at every corner of the world. For example, in Australia and N. Zealand, there has been a study mentioning a ratio of 1 for 86,000 births (Adam, 2015).

3. Causes

The syndrome was firstly described as one of unknown cause, since no particular cause had been noticed. Milunski and Huang, in a study published in 2003, first noticed some issue with cell reproduction in 6 people diagnosed with Kabuki syndrome, who had no family relation and came from different tribes. Their different tribal origin was initially considered as a statement of common causative basis for the syndrome (Milunski & Huang, 2003). After this finding, Milunski cooperated with other research teams, in order to discover the same finding.

One of the first researches that attempted to relate the cause of the syndrome to gene mutations was that of Ng. Specifically, Ng with 20 more researchers, with Norio Niikawa (who had first described the syndrome) among them, regarded the mutations on the MLL2 gene to be the primary cause of the Kabuki syndrome (Ng et al., 2010).

A few years later, a new research was published by more than fifty researchers and with dozens of research centers participating (Makrythanasis et al., 2013). The "incriminating" role of the MLL2 gene had already been detected and researchers attempted to confirm this and to determine whether there is some relation between genotype and phenotype resulting from the particular mutation, by studying 86 people with Kabuki syndrome. The researchers used a weighted phenotypic list that included typical characteristics of the syndrome, such as arched eyebrows, ear malformation etc. and thus they selected the 86 people who took part in the research. 45 of them had mutations on the MLL2 gene and showed the most serious characteristics of the syndrome. In general, those who had any kind of mutation on the MLL2 gene got higher score in the phenotypic list, compared to the rest of the participants. In specific, they had intellectual disability at a greater percentage compared to those without the particular mutation, developmental anomalies, short stature and heart diseases. It is also interesting that there has been at least one more incriminating gene found, the KDM6A gene (Makrythanasis et al., 2013). More particularly, the majority of the people diagnosed with Kabuki syndrome showed mutations on these two genes. 55% to 80% of them had mutation on KMT2D (former MLL2) and 12% on KDM6A. There was also a 10% to 20% of the people with the syndrome, who did not have some kind of mutation on these genes. The phenotype of the people with mutation on the KDM6A gene showed some differentiations. For example, women with KDM6A mutation appeared to have milder phenotype compared mainly to men with mutation either on KMT2D, or KDM6A, with the women's Intelligence Quotient ranging from standard intelligence to marginal intelligence (Adam, 2015).

4. Characteristics

Kabuki syndrome is recognized as a birth defect, characterized by specific face features, intellectual disability at various degrees, skeletal abnormalities, congenital heart diseases, swollen fingerprints and short stature (Adam, 2015). Other characteristics include: renal failure, lung disease and dermatological rashes. The face characteristics include: large arched eyebrows with a long palpebral fissure, large and dysmorphic ears, broad nasal tip, dental abnormalities, hypodontia, cleft palate, strabismus, eyelid drooping, blue eye coat, micrognathia, thin upper lip. Of course, facial dysmorphism tends to become less apparent over time, with the exception of the large eyelid fissures that remain (Makrythanasis et al., 2013). The distance between the nose and the mouth is usually long (Kasdon & Fox 2012). The ears, besides being dysmorphic (large and protruding), are low-set and the forehead is wide (Muluk, Yalçınkaya, Budak, Gündüz & Ayas, 2009).

As far as the central nervous system is concerned, hypotonia, epilepsy and microcephaly are often observed. Furthermore, there have been several cardiac system malfunctions, such as in the mesothelial communication and aortic stenosis. There are also many eye problems, such as spots on the iris, lagophthalmos, corneal erosion and strabismus (Chen, Sun, Hsia, Lai & Wu, 2014). In addition, gastrointestinal disorders like regurgitation and serious feeding problems are observed. A number of problems are observed at the oral cavity as well: hypodontia (sparse dentition), cleft lip, cleft palate (Adam, 2015). Among others, anomalies in the tracheobronchial tree causing pneumonia and asthma have been observed in the respiratory system (Lai et al., 2014).

There is no prenatal or postnatal examination to diagnose the syndrome apart from the individual's clinical picture. In 1988, Niikawa, who was the first to describe the syndrome, studied 62 patients and suggested 5 diagnostic criteria (Cuesta, Betlloch, Toledo, Latorre & Monteagudo, 2001). These five basic characteristics are: distinctive facial features, dermatological rashes, skeletal abnormalities, mild to moderate intellectual disability and short stature (Santos, Ribeiro, Stuani, Silva & Queiroz, 2006).

5. Neuropsychological skills

People with Kabuki syndrome very often show malfunctions of the central nervous system. Even though the syndrome is commonly associated with intellectual disability, a small number of people with Kabuki syndrome may have typical intelligence. The adaptive malfunctions of a person with Kabuki syndrome remain in their adult life too. According to Sanz et al. (2010), the successive neuropsychological assessments depict a person's developmental progress better than an instant assessment that may lead to incorrect or incomplete descriptions. Therefore, in 2010, they presented a research on the developmental progress of a 12-year-old girl with Kabuki syndrome, through multiple developmental and psychological assessments that were carried out when she was 4, 6, 7, 9 and 11 years old. This girl used hearing aids from the age of 5, underwent a strabismus operation when she was 10, had visual-motor impairments and was diagnosed with Kabuki syndrome when she was 10. Generally, she showed motor delay regarding crawling and walking, language and social skills development delay. She showed sensory sensibilities, rigid thought and adherence to routines. Her reading skills were on the average of her peers, whereas her numeracy skills were below the average of her peers. At the age of 10, she suffered from anxiety and depression and she was treated with sertraline. As far as her behavior is concerned, she was a friendly kid, with a good, consistent and happy mood (Sanz et al., 2010). She was cooperative in all assessments, always trying to have incentives. At the age of 4, she occasionally showed stereotypical behaviors (hand flapping) as a reaction to happiness or enthousiasm, behaviors that were not observed in the next assessments. Being overactive, impulsive and restless did not seem to affect her performance. Her intellectual functions were assessed by two tools, the Stanford-Binet at first and then the WISC-IV. At the age of 4 and 6, her performance was on the average of her peers. At the age of 9, it dropped below the average and at 11 it was marginal. However, in the overall assessments, the girl did not seem to lack skills; on the contrary, she continued gaining new ones, only she did this at a slow pace. Her language and communication levels were adequate, though there were some articulation problems. Her language and verbal memory levels remained constant in all assessments, maintaining a relative rise that placed her among the higher average of her peers. On the contrary, the visual perception, visual-motor skills and visual memory steadily dropped over time. In the fields that she gained new skills, this occurred more slowly than expected for her age. Her adaptive skills and self-care have always been below her peers' level. In conclusion, through this case study, it seems that the language skills of a person with Kabuki syndrome are on the average of their peers and increasing over time. On the other hand, their visual skills decrease steadily from the age of 9 onwards.

6. Language

People with Kabuki syndrome have various issues regarding speech. A clinical research in the Netherlands investigated the communication development and linguistic difficulties of people with Kabuki syndrome. Its subject were six kids (3 boys and 3 girls) aged from 4.4 to 10.6 years old. Its research material consisted of samples of unforced and spontaneous talking which were analyzed by a Dutch standardized diagnostic tool that evaluated different aspects of spontaneous speech production. Findings showed deficits in all six kids and in all linguistic fields, such as phonology, morphology, syntax, semantics and pragmatics (Defloor, Van Borsel, Schrander – Stumpel & Curfs, 2005).

Several linguistic problems were also recorded in another research which investigated the issue on an Indian, 7-year-old, illiterate boy with IQ 71 and Kabuki syndrome. More particularly, they evaluated his flowing and spontaneous speech by the use of an Indian standardized diagnostic tool. His receptive language skills were within normal limits, whereas his expressive language functions were below the average of his peers. He lacked articulacy, largely due to hypotonia and poor kinetic coordination of parts of his mouth during articulation. He often used grimaces when talking. He could follow complex orders and utter phrases larger than 3 words with simple structure and grammar mistakes.

His receptive vocabulary ranged from 1,200 to 2,000 words, whereas his expressive vocabulary ranged from 800 to 1,500 words. He would take initiatives for a dialogue or information exchange. His talking could be characterized as monotonous and boring. Although he had good phonological awareness both in distinguishing as well as in producing phonological units, he made mistakes in prosody and articulation when in flowing talking. As far as semantics is concerned, he was good at naming and lexical classifications. On the other hand, he faced difficulty in synonyms, homonyms, antonyms and the relations of paradigmatic and syntagmatic axis. He also got low scores in syntax, making several mistakes especially when the syntactic structure of the sentence became more complex (Malik, Sharma, Sakhuja, Munjal & Panda 2010).

As far as the pragmatic use of language by people with Kabuki syndrome, a relevant research, which focused on the language profile of a 4-year-10-month-old boy with Kabuki syndrome and standard intelligence, showed that he could use the language in satisfactory pragmatic level within simple, everyday circumstances. However, when he had to communicate in a non-protective environment and more complex and unfamiliar social circumstances, his pragmatic skills were deficient (Muluk et al., 2009).

In general, people with Kabuki syndrome show difficulty in both receiving as well as expressing language. Language development is often delayed and there are quite a lot of syntax mistakes. This may be due to the recurrent ear infections that almost 63% of children with Kabuki syndrome experience, and which lead to reduced or loss of hearing, therefore making language acquisition even harder (Kasdon & Fox, 2012).

7. Kabuki and Autism Spectrum Disorders

Several people with Kabuki syndrome have been diagnosed with Autism Spectrum Disorders too. More specifically, children with Kabuki syndrome often show particular behavioral characteristics, which diverge from the standard social skills of the typically developing individuals. For instance, 30% of them interact poorly with others, whereas 74% show a particular preference for routines (Malik et al., 2010). The Akin Sari, Karaer, Bodur, & Soysal, (2008) research sheds light on the relation between autism and the Kabuki syndrome, as it focuses on a child with Kabuki syndrome, high IQ, autism and hyperlexia. This boy was diagnosed at the age of 2 years and 2 months old, when his parents noticed delayed speech development, little eye contact and difficulties in interaction with peers. When examined, he showed stereotypical behaviors, such as hand flapping, echolalia, obsessions with behaviors (for example interest in car or device brands, rotation of his toys' moving parts) and toe walking. His intelligence was measured with the Stanford – Binet scale and was found to be IQ 123. The Denver II Developmental Screening Test showed that his personal and social skills, as well as his fine motor skill were delayed for his age. The aforementioned characteristics were confirmed in a diagnostic assessment that followed when he was around 3. Furthermore, repeated speech and hyperlexia were observed. Despite his young age, he could read a few words, though not understanding their meaning. He was diagnosed with autism, based on the criteria of DSM-IV. The same research makes reference to more cases of people with Kabuki syndrome and Autism Spectrum Disorders at the same time.

According to Kasdon & Fox (2012), there are several people diagnosed with both Kabuki syndrome and Autism Spectrum Disorder. There are even more people who have Kabuki syndrome and show similar behaviors to those of autistic people, such as social inappropriateness, interpersonal disorders, communication difficulties, few and particular interests, stereotypes and emotional disorder.

8. The case of student X

Student X was an 8-year-old boy in the region of Epirus (Greece) who possessed almost all the aforementioned characteristics. More particularly, he was diagnosed with Kabuki syndrome in a state hospital. When he was 9 months old he experienced an incident of loss of consciousness. At the age of 3, X appeared nervous, responded only to very loud sounds or voice, did not fully execute orders, did not get up from seated position, walked supported and did not have control of his sphincters. He was given the WISC-III intelligence test when he was 7 and he was found to have marginal intelligence. Today, he still has some psychomotor retardation, he has gained control of the sphincters, he walks satisfactorily but a bit unsteadily, and he executes orders. He has recently started visiting the speech therapist and the occupational therapist. Going to the kindergarten was problematic and often interrupted.

X has normal weight and relatively short stature for his age. He also has the typical characteristics of the syndrome, arched eyebrows with the palpebral fissure, big and malformed ears. In his oral cavity, he has problems with his teething and was born with cleft palate, which he was operated for in the past. He uses hearing aids because of his moderate hearing loss (he was diagnosed at the age of 4, after an audiological test). Another physical characteristic is the dysplasia of his limbs, causing difficulties in fine and rough motion.

He is quite social and can easily separate from his parents. He shows a positive mood and develops interpersonal relations distinguished for their emotional stability. He responds positively to reward and he seems to pursue it. He particularly expresses his feelings, positive as well as negative ones. He seeks hugs, physical contact (caresses) and he is very effusive in acts of love. He tries hard to approach his classmates, especially during breaks, although his classmates do not always respond. They usually avoid playing with him, due to the lack of communication between them. What is special in his social profile, is his extreme "intimacy" in approaching others, younger or older.

He is very good at miming and executes most orders. He knows the basic body parts. He can distinguish the basic colors and shapes. He likes looking at pictures paging through books and he can concentrate for long time. He manages fairly well with everyday living activities and he seems to easily follow school routines, especially when he has realized their objective. He has poor, short-term memory. As far as cognition is concerned, he lags behind his peers, particularly in Language and Maths.

Due to X's difficulties in learning, from his first year in Primary School it was suggested to his mother that he attend a complementary programme of personalized instructional intervention within the school's running, but she initially refused. In the next year, when his mother ascertained her son's difficulties in Language, she agreed to her son's participation in the suggested intervention programme.

9. Instructional Intervention

The educational assessment found that X showed deficiency in phonological awareness and he had not acquired the mechanics of reading. More particularly, regarding consonants, he had difficulty in matching phonemes-graphemes, especially those that looked or sounded similar. He found it particularly hard to recognize and produce the 4 Greek consonants /v/, /ð/, /θ/, /f/ (Holton, Mackridge & Philippaki-Warburton, 1997). Additionally, X could not read syllables, consonant combinations and diphthong vowels. While reading, he found it hard to locate the space-time frame of a text and to use time expressions.

As far as Maths is concerned, his performance in addition and subtraction with ten was tested, as well as in solving a simple problem. He appeared to have difficulty in operations within ten and in solving problems, even of just one operation.

Due to his severe difficulty in reading, it was decided to focus the intervention on reading skills. Specifically, priority was given to the correct matching of all phonemes with the corresponding graphemes of the mother tongue, and to the reading of simple syllables of the consonant-vowel (CV) structure, in random columns of 10 syllables and in less than 2 minutes. The time target for reading ten syllables was set to 2 minutes, after timing his reading ability, where it was found that X could hardly read ten syllables in 5 minutes. Since timing is a procedure that may cause overstimulation to the student, there were two researchers in the class, one of them timing without being noticeable by the student.

The intervention was carried out in 2 stages: at first, the intervention focused on distinguishing the letters and then on reading corresponding syllables. Beginning with distinguishing the letters, it was attempted to connect mainly the letters that were difficult for X with some natural sound, telling him a short story. For instance, in order to learn the letter /f/, he was asked to mime the sound of the wind or some kid blowing their birthday cake candle. Laminated cards 5x5cm were later used, and X was each time asked to identify the consonant-target from a group of 2 consonants, which gradually included 6 consonants. He was then given random syllables, being each time asked to circle the consonant-target.

After the identification tests were completed, X was given production tests. He was asked to write the letter-target in a multisensory way. That is, to write the letter on the board, on a piece of paper with pencil, on a sketchbook with felt tip, in the air, on sand, to make the letter with plasticine etc.

He was then given tests on identifying and producing syllables. In the first ones, X was given laminated cards with the consonants he had difficulty in identifying and, next to them, the researchers placed all vowels randomly so that all possible syllable combinations were formed. X had to read the syllable. When he could not, the researchers helped him indirectly, reminding him the sound of the initial letter. So, if X could not read /fa/, one of the researchers would say: "how do we blow a birthday candle?" so that he remembers /f/. In this stage, the researchers also used the syllable table. This is a dual entry table, which has consonants in the first column and vowels in the first row, so that all possible syllable combinations can be made.

Then, X was given syllable production tests. He had to form the syllable he heard with the cards. There was a pile of cards with syllables, both with the consonant-target as well as with other random consonants combined with vowels, and he had to choose the correct ones. In the end, he had to write the syllables that the researchers told him on the board.

At the same time, phonological awareness tests were conducted at the level of the syllable and the word. Phonological awareness is known to be associated with an individual's reading ability and the reading problems. The "games" that boost phonological awareness, enhance reading and writing skills (Bradley & Bryant, 1983). At first, synthesis and analysis tests were given. For example, a researcher uttered, slowly and with a pause between them, two simple syllables consisting of consonant-vowel (CV) and X had to say the word that the two syllables form (synthesis), or, respectively, X listened to some two-syllable word and had to analyze it into its syllables (analysis).

Then, he was given identification and production tests. In the identification tests, X had to find and say words or syllables beginning with the consonant-target. The researchers uttered three words and X had to identify the two words that begin with the same syllable.

As far as the evaluation of the instructional intervention is concerned, it was in two stages. The first stage was to assess X's reading skills. In particular, he was asked to identify and write (production) several consonants. After locating the consonants that he had difficulty with on both levels (letter and syllable), the intervention programme began. When the intervention was completed, the second stage of the evaluation was conducted and it showed that X could answer correctly, getting over 90%. The first goal was therefore considered achieved.

The second goad, which was also harder, was evaluated by timing syllable reading in columns (10 syllables/column). Like said before, at first X exceeded the 5 minute limit without completing to read all 10 syllables of the column. Gradually though, after continuous repetition, he managed to read random columns with syllables in less than 2 minutes for each column, showing that this goal too was achieved. The intervention lasted 6 months in total, with 1-2 teaching hours daily (45 minutes/hour).

It is therefore proven that the principles of instructional intervention that are used in the teaching of people with intellectual disability – such as step by step learning, project analysis method, repetition, etc. – can be successfully applied in Kabuki syndrome.

10. Research Limitations

The sample size constitutes a major limitation of the present research. Of course, the Kabuki syndrome rarity explains why most relevant articles present mainly case studies or just a small number of research subjects. Another limitation of this attempt is that it did not check whether the person with Kabuki syndrome maintains their performance after the completion of the instructional intervention that was applied. Additionally, family was not sufficiently exploited as teaching framework.

11. Suggestions for future research

The scarcity of the syndrome and the identification of people with it, require the organizing of a relevant institution, both national and international, to support them properly. Although Kabuki syndrome is associated with gene mutations, there is still a percentage (10% - 30%) of unmapped reasoning, suggesting the need of further research on the field. Furthermore, the language level of people with Kabuki syndrome requires further investigation, since the syndrome seems to influence language, speech in terms of phonology and articulation, and, generally, the linguistic perception and expression. However, the existing relevant articles do not agree on which part is affected more. Based on the social profile of people with Kabuki syndrome, it appears that they show difficulties in interacting with their peers, lack of communication and poor social skills. It is therefore necessary to further investigate how to boost their social skills.

In conclusion, Kabuki syndrome is still today a "terra incognita" field. However, it is crucial that those involved in fostering people with disabilities investigate further the matter, so that our fellow humans with Kabuki syndrome manage to live a better life.

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